EMERGING TECHNOLOGIES AND THEIR IMPACT
November/December 2006
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Technology Review

AN MIT ENTERPRISE

Will This Save the World?

The $100 Laptop

BY JAMES SUROWIECKI Page 48

technology
review
Published by MIT

The world consumes two barrels of oil for every barrel discovered.

So is this something you should be worried about?

The fact is, the world has been finding less oil than it's been using for twenty years now. Not only has demand been soaring, but the oil we've been finding is coming from places that are tough to reach. At the same time, more of this newly discovered oil is of the type that requires a greater investment to refine. And because demand for this precious resource will grow, according to some, by over 40% by 2025, fueling the world's growing economic prosperity will take a lot more energy from every possible source.

The energy industry needs to get more from existing fields while continuing to search for new reserves. Automakers must continue to improve fuel efficiency and perfect hybrid vehicles. Technological improvements are needed so that wind, solar and hydrogen can be more viable parts of the energy equation. Governments need to create energy policies that promote economically and environmentally sound development. Consumers must demand, and be willing to pay for, some of these solutions, while practicing conservation efforts of their own.

Inaction is not an option. But if everyone works together, we can balance this equation. We're taking some of the steps needed to get started, but we need your help to get the rest of the way.

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The world consumes 84 million barrels of oil a day.

By 2030 the number of cars in the world will increase by 50%.

World Energy Demand

2000 2050 2100

Chevron Steps Taken:

Thinking to the future:

- Committing more than $300 million each year on clean and renewable energies

Finding even more energy today:

- In 2004, achieved exploration record 78% higher than 10-year industry average
- Using steamflooding to extract heavy oil that was previously unrecoverable – more than 1.3 billion barrels from one field alone

Chevron

Human energy

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Cover photo by Christopher Harting

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23 Years Ago in *TR*

Only Kentucky matches federal SBIR-STTR Phase 1 + Phase 2 awards

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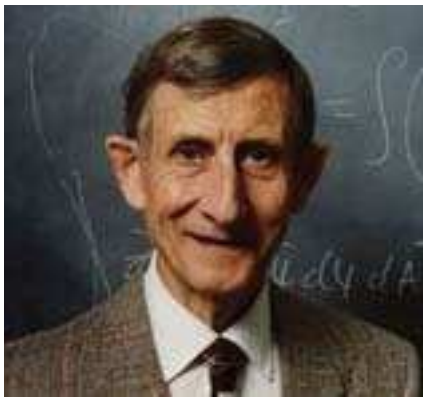


Freeman Dyson wrote the first of what will become regular features in this magazine: essays. In "A Failure of Intelligence" *(p. 62)*, Dyson recalls the time he spent, beginning at age 19, developing analytical methods to help the British Royal Air Force more safely and effectively bomb German targets. "Now that we are engaged in an unpopular and badly mismanaged war," he says, "people have a tendency to look back on World War II with nostalgia as a 'Good War,' fought with a clear moral purpose and competent management. Since I belong to the dwindling group of survivors with personal experience of World War II, I wrote this piece to give the younger generation a glimpse of that war as I saw it. From my viewpoint at the headquarters of Royal Air Force Bomber Command, the war was a meat grinder, slaughtering German civilians and British airmen with equal mindlessness, paying little attention either to moral principles or to strategic needs. In that war as in the present one, secrecy was used to conceal our failures and mistakes, not so much from our enemies as from our own citizens." Dyson was for many years professor of physics at the Institute for Advanced Study in Princeton, NJ. He is famous for his work in mathematical physics and as an author of books for the general public, including his classic intellectual autobiography, *Disturbing the Universe*.

James Surowiecki wrote this issue's cover story *(p. 48)*, which explores the work of Nicholas Negroponte and his philanthropic organization One Laptop per Child. Negroponte, Surowiecki argues, has done more than build the now fabled $100 laptop: he has also created a philanthropic organization

that might do for the early 21st century what Andrew Carnegie's push for public libraries did for the early 20th. "At least to my mind," he says, "philanthropy and charity used to feel like pretty sleepy topics. But I think today, the nonprofit sector really has become home to some of the most interesting and innovative thinking about everything from education to health care to development, and the $100-laptop project epitomizes that shift." Surowiecki is the financial columnist at the *New Yorker* and the author of *The Wisdom of Crowds*.

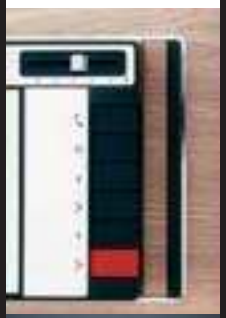
Horace Freeland Judson writes in this issue about the current state of gene therapy *("The Glimmering Promise of Gene Therapy," p. 40)*, a field whose false starts and dashed hopes he has been watching for much of his career. "I have been tracking recombinant DNA and the hopes for gene therapy for more than a third of a century," he says, "with an archive of interviews of almost archeological proportions, going back as early as 1970." Judson has held academic appointments at Johns Hopkins and Stanford Universities, and he founded George Washington University's Center for History of Recent Science. He is the author of *The Eighth Day of Creation*, a history of molecular biology whose first three chapters appeared in the *New Yorker* in 1978. He recently signed a contract for a book that will expand on the story he tells here.

Wade Roush wrote the review in this issue of MySpace *(p. 72)*, the world's most populous and possibly most marketing-ridden social-networking website. "I've been covering the culture and technology of social computing for a few years now, including the social-networking sites, but I'd never written about MySpace," he says. "It's the elephant in the room that the inventors of social networking would rather disown, and I understand why.

It's garish and chaotic. But more than that, the site pushes members to define themselves in terms of the songs, videos, and products they're consuming, rather than as individuals with unique interests. It's a giant incubator for viral marketing, with members as the vectors." Roush earned a PhD in the history of technology from MIT in 1994. He recently moved from San Francisco, where he spent five years as senior editor and West Coast bureau chief for *Technology Review*, to Las Vegas, where he has taken up a freelance career.

RECORD

8-TRACK



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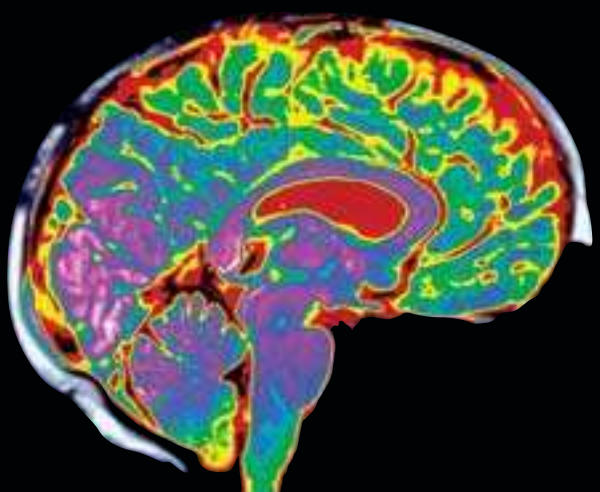

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Letters

Our September/October 2006 issue featured our annual presentation of the TR35, our list of 35 noteworthy innovators under the age of 35.

The TR35

Matthew Herren's vision of enabling educational opportunities for young Africans is to be applauded for focusing on the most disenfranchised people in the world *("TR35: Young Innovators with This Year's Best Ideas," September/October 2006)*.

I believe there is a blind spot in Mr. Herren's vision, however. He argues that many paper-based educational materials are far beyond the means of many poor families, and that the solution to this problem is to switch from paper-based media to electronically based media—and yet he doesn't say how such a switch would reduce costs. Electronic delivery mechanisms require power, via battery or dedicated electrical-transmission lines. I can state from experience that the overwhelming majority of Africans have no access to electricity and could not power their electronic learning-delivery devices even if they could afford them.

I applaud Mr. Herren's vision, but I think he may have more obstacles in his path than he might anticipate. Nonetheless, as your magazine so eloquently points out, true innovators are not discouraged by obstacles, and I sincerely wish Mr. Herren success in his pursuit.

Jim Lewis
Bel Air, MD

TR35 member Michael Raab's bioengineering approach toward economical ethanol production, which centers on infusing corn with enzymes that will allow more of the plant to be converted into ethanol, needs the following modifications: transfer this work to common lawn grass, and politically mandate the periodic gathering of the clippings for ethanol production. Using every homeowner as a source for agricultural production would free up our croplands for more vital uses!

Thomas S. Stein
Neenah, WI

In reading your roundup of this year's TR35, I noticed a lot of very interesting things in the area of neurology. However, I was disturbed that so many of the experiments you described used mice. Mice experience fear and suffer pain and death in the laboratory, and yet you never question whether it is ethical to use them. I won't claim to know the right answer, but I do know that scientists must always question the ethics of their methods. If pursuing knowledge harms others, it is not acceptable to do it just because one can. I hope in the future you at least discuss the ethics of the means your TR35 use.

Eric Walden
Lubbock, TX

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Please include your address, telephone number, and e-mail address. Letters may be edited for both clarity and length.

Why is youthfulness so important? What is wrong with just naming the 35 best innovators and, if they are predominantly under 35, commenting on it? The three Bell Labs inventors of the transistor were all over 35. This youth worship is ridiculous. How many times has a company appointed a seemingly young, lively, innovative, energetic, free-spirited senior executive or R&D specialist and then regretted it?

Jason Pontin writes, in his September/October 2006 editor's letter, that successful innovators "*appreciate* failure." It is true that development can be unrewarding if goals are set too low, and that setting goals higher increases the chance of failure. But if supposed innovators are familiar with and appreciate failure at a young age, beware.

Frank Haneman
Clinton, CT

Energy and the Environment

The energy plan you lay out in your editor's letter introducing the July/August 2006 issue's special report *("It's Not Too Late")* simply considers how to meet the projected increasing energy demand of an insanely materialistic society with a huge environmental footprint; it never considers the consequences. Any reduction of energy-related greenhouse gases achieved through your plan would be more than offset by other increases in greenhouse gases and other environmental impacts caused by the expanding economic activity your plan seeks to protect. You are promoting business as usual, except that carbon dioxide from energy production is to be reduced. This plan won't get us where we want to be. We need basic structural changes in the American lifestyle and economy.

You err as well, and most dangerously, in your assumptions that the heavily materialistic and unhealthy American lifestyle is nonnegotiable and that the poor of the world just can't wait to get their hands on McMansions, SUVs, and plasma televisions. Polls, in fact, show Americans to be willing to pay more in taxes, and more for products and services, if it will protect the environment. And the rest of the world is getting increasingly impatient and angry waiting for the people of the "rich world," the United States in particular, to start living in a responsible and sustainable manner. Read the newspapers, especially the foreign press, for gosh sakes. Or get out of Cambridge and do some traveling.

Dennis Sebian
Kirtland, OH

Correction: Our story on Roger Dingledine's Tor Project *("TR35: Young Innovators with This Year's Best Ideas," September/October 2006)* indicated that people can use Tor to send e-mail anonymously. Tor is designed to create a nontraceable, two-way circuit for applications such as Web browsing, instant messaging, and uploading content to a blog or other website. Tor will mask the origin of e-mail sent through Web-based services, such as Gmail, but to avoid facilitating spammers, it is not set up to act as a relay for anonymous e-mail. *Technology Review* regrets any confusion.

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C. Total paid and/or requested circulation:	239,596	215,231
D. Free distribution by mail:	2,490	2,252
E. Free distribution outside the mail:	5,124	6,636
F. Total free distribution:	7,614	8,888
G. Total distribution:	247,210	224,119
H. Copies not distributed:	17,271	26,683
I. Total:	264,481	250,802
J. Percent paid and/or requested circulation:	96.9%	96.0%

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(Signed) Heather Holmes, Director of Circulation

In Praise of Print

Where traditional magazines are better than the Web

This month, we introduce a new section of the magazine. It's not one that would work well on our website. Had I asked you, our readers, if you wanted such a section, you likely would have said No.

Every issue, we will publish an essay, memoir, or short fiction. They will shine some indirect light upon emerging technologies, our ordinary subject matter. But they represent a departure for us; our longer features have been conventional investigative or explanatory articles.

The first of these essays, "A Failure of Intelligence" *(p. 62)*, is an account by the renowned theoretical physicist Freeman Dyson of his time in the Royal Air Force's Bomber Command, during the Second World War. He describes the ingenious mathematical techniques he devised to evaluate the technologies employed by British bombers of the era. (To understand why Dyson thinks his story is relevant today, read his contributor's note on page 4.)

I would *never* have commissioned such a piece for technologyreview.com. For a start, the essay is very long, and almost no one reads long stories on a computer, or even prints them from a Web page. Secondly, it is only slyly topical, and the Internet is mostly unforgiving of stories that are not bluntly of the moment. Finally, it is not obviously useful, and search engines and hyperlinks promote stories that answer people's questions and gratify their preoccupations.

In short, the Internet is a very good medium for economically expressed, timely stories. More, the Web is unapologetically responsive to the market. Online, the posture of editors before readers is slavish: we listen to your demands, or else we (more tangibly, our "audience traffic") are punished.

Yet editors can do more than give readers what they say they want; they can also offer up stories that surprise and delight. In print, editors can be purveyors of serendipity. Such a function may not be wanted in the yawping, demotic marketplace of the Internet. It can seem unacceptably elitist to those who are skeptical about the intelligence, expertise, impartiality, and good sense of what the blogosphere calls the "mainstream media." But there are still many readers who will pay for that old-fashioned virtue, nicety of editorial selection.

A print subscription is a contract, in which the reader trusts the editor to deliver a type of journalism in every issue. A magazine reader does not "search for content" but arrives, like a punter at a favorite bar, pleasurably anticipating a familiar experience. Yet because a magazine is a discrete package, a reader will welcome the odd, novel addition to the usual fare, provided it is aligned with the magazine's editorial mission and (for a publication like *Technology Review*, at any rate) is knowledgeable, well written, intelligent, and civilized.

When I became the publisher of *Technology Review*, I explained that we were reducing the frequency of our magazine to six times a year and increasing the number of stories we published online *(see "From the Editor," December 2005/January 2006)*. Many of you thought I was panting to abandon print. It wasn't true. I love magazines. I think modern publishing companies must offer their readers and advertisers a variety of media; but there are some things that magazines do best.

Write and tell me what you think of Freeman Dyson's essay at jason.pontin@technologyreview.com. **Jason Pontin**

MARK OSTOW

High-Speed Railways in Spain

By Cynthia Graber

Spain is rapidly expanding its high-speed rail service, becoming one of most connected countries in the world. As the high-speed rail network grows, Spanish companies continue to innovate and provide new services and products at lower prices to meet the world's growing demand. This is the fourth in an eight-part series highlighting new technologies in Spain and is produced by Technology Review, Inc.'s custom-publishing division in partnership with the Trade Commission of Spain.

The sensation of riding on Spain's high-speed rail from Madrid to Seville is more than anything one of smoothness, without the bumps and jostles common on conventional rail. The journey passes so comfortably, in fact, that it's easy for a rider to forget the speeds at which the train is traveling—unless, of course, the rider happens to stand in the conductor's cabin. From the conductor's vantage point, scenery zips alongside as tunnels loom ahead, then the train quickly plunges into darkness before darting out once again into the light. The speed, the most important trait of high-speed rail, turns from simply a number on paper into something visceral.

Spain has embarked on an ambitious project to develop high-speed rail connections in every major city, spanning out in a web all around the country and connecting the urban dots along the coast. By 2020, the country plans to have 10,000 kilometers of high-speed rail completed, placing 90 percent of the population within only a few dozen kilometers of a high-speed rail line and shooting Spain to the world's top ranks in terms of total high-speed rail on the ground.

In the process, Spanish industry has taken advantage of the country's new focus on high-speed rail to develop new products to meet the demand of Spanish market, and to innovate and compete on the world market for parts and services.

What Is High-Speed Rail?

The history of rail is long and varied around the world, and definitions of "high speeds" have changed dramatically over the years. Railways had a monopoly on passenger travel throughout the late 1800s and early 1900s at speeds that were considered rapid at the time—about 100 kilometers per hour.

A high-speed train whizzes across a bridge in the Spanish countryside.

After World War II, the United States came to rely on improvements in cars, highways, and air travel, while Europe and Japan focused on rebuilding and improving the railway system. Higher-speed trains were originally imagined in order to win back large numbers of passengers who had been diverted to road and air traffic (reasons similar to those motivating Spain today).

Today, "high speed" trains are generally understood to be those that travel at and above 200 kilometers per hour, or 124 miles per hour. That speed was first reached by a Japanese train, which was officially launched in 1964. France's TGV followed in 1981. Actually, 200 kilometers per hour is now considered relatively slow in the high-speed world: most high-speed trains today travel at 250 to 300 kilometers per hour (150 to 185 miles per hour). Trains are in development that run at 350 kilometers per hour, and on test tracks, trains have reached more than 500 kilometers per hour.

The term "high-speed rail" does not refer to a particular type of train but, rather, simply to the speeds it can attain. Today most high-speed trains are electric, though diesel trains, incorporating newer technology, have been able to reach similar speeds. For instance, the Spanish company Talgo has a diesel train that reached 250 kilometers per hour in testing, though its trains purchased for systems around the world remain electric.

History

The history of high-speed rail in Spain began two decades ago, in 1986, when the government decided to further the country's investment in rail. At the time, involved officials in Ministries of Economy and Transportation and the office of the President debated whether to develop improved and additional conventional rail lines or take the plunge with high-speed. Spain has a particularly high density of air travel, with each regional capital having its own airport, and the government determined that high-speed rail presented the best economic and environmental alternative to attract people away from planes and cars.

As to where that first line would run, the government chose the Madrid-Seville route. Though it might seem less logical than linking the two major economic centers, Madrid and Barcelona, a number of factors made this track a clear first choice. Before 1986, traveling to Seville from Madrid meant a long, indirect route over a single-track rail. "This was technically the most important bottleneck in the network," says Joaquín Jiménez, director of international relations for ADIF (the Spanish acronym for the Railway Infrastructure Administrator). Says Jiménez, "This line was the one where, with the least investment, we could dramatically cut the distance for the largest number of passengers by building a new line entirely, not running parallel to existing train lines." In addition, the World Expo planned for Seville in 1992 gave the government a time and goal to work toward.

There were practical economic reasons to choose Seville for the first destination. That same year, 1986, Spain entered the European Union. With the entrance, the Spanish government had access to EU funds for infrastructure development, and the government decided to invest in the development of the relatively impoverished region of Andalusia.

The construction of the line was hampered by the need to cross the Sierra Morena mountains. "Spain is the second most mountainous country in Europe, after Switzerland," says Juan Matías Archilla, director of international relations for Renfe, the Spanish rail operator. Today, improvements in tunnel engineering assist in the development of shorter rail lines; Spain is currently building one of the longest rail tunnels in the world north of Madrid, crossing the Sierra de Guadarrama along the new high-speed route between Madrid and Valladolid and serving the entire northwest of Spain.

It took only six years for the 471-kilometer line to be completed, an unusually short time for a line of this distance. It cost about a third less than similar lines—in part because of the dogged commitment of the local and national government to achieving the goal in time for the World Expo.

After the trains finally reached optimal speed, it took just two hours and twenty minutes to reach Seville. Before, any rail traveler would spend nearly triple that, about six hours. Riders soon arrived in droves, and the line proved to be a crucial link in the economic development of the region.

After the success of the Madrid-

Seville line, the economic crisis of 1993 hit Spain, along with much of the rest of the world. It wasn't until 1997 that the country found itself on strong enough economic legs to return to the theme of high-speed rail. The view automatically turned to developing the route between Madrid and Barcelona, with the idea of cutting travel time from six and a half hours down to about two and a half.

In 2003, the next line of Spanish high-speed rail (known by the Spanish acronym AVE) opened in Spain: from Madrid northeast to Lleida, which is the beginning of the lines both to Barcelona (to open in 2007) and to the French border. The trip time was reduced by half. By early 2005, a shorter-distance high-speed line opened up southward from Madrid to the nearby town of Toledo. By the end of 2006, the southern lines stopped along the coast; they will reach the popular tourist destination of Málaga by 2007. Construction is already in advanced stages for lines reaching the Mediterranean coast and the French border.

Why Rail?

As Spain strengthened its economy in the 1980s following its emergence from economic isolation, the decision about how best to invest in infrastructure development became paramount. Rail offered a wide variety of benefits. Development of rail, it was determined, provided the best means for increasing economic development in the outlying areas of the country by providing speedy and straightforward travel between cities, while addressing environmental concerns. "Until 1986, rail had been languishing," says Jorge del Fresno, vice president of Ineco-Tifsa, a rail consulting and engineering company. "It had been doing worse and worse because people weren't satisfied with the rail service, and they turned increasingly to roads and planes."

The decision to invest in high-speed rail also came about in part because of a need to reduce greenhouse gases under Spain's participation in the Kyoto Protocol. Rail, which runs on electricity (and electricity in Spain is partly generated by renewable sources such as wind), is significantly cleaner than either planes or cars. The data for the Madrid-Seville line support the investment in high-speed rail: before the advent of the new line, 11 percent of passengers traveled to Seville by plane and 60 percent by car. After the AVE began service, only 4 percent traveled by plane, 34 percent by car, and more than half on the train.

"With rail and the use of significantly cleaner electricity," says Jiménez of ADIF, "our dependence on petroleum is greatly reduced."

According to Spanish government studies, consumers can be convinced to

High-Speed Railways in Spain

This map shows existing high-speed rail lines, those under construction, and the plans for 2020. By that time, Spain will be covered by a web of high-speed lines stretching into both France and Portugal.

switch to rail if the journey is as short as two and a half hours. Any minor reduction in time past two and a half hours does not significantly increase passenger demand along the line. "What we've found is not that the passengers need to arrive even more quickly," says Jiménez, "but that they want access to the city centers in a timely fashion. Our stations have an advantage over flying due to their placement."

The government has also studied public response to high-speed rail, and in general the response is highly favorable. In addition to the comfort and ease of travel, the line from Madrid to Seville offers the only money-back policy in the world that refunds the entire fare if there's even a five-minute delay. The policy was implemented in 1994, two years after the Madrid-Seville line opened, and less than 0.25 percent of all trips since then have resulted in a return of ticket fares. (Though that assurance has not yet been implemented in all the newer lines, representatives say the goal is to have every high-speed rail line in Spain carry the on-time guarantee.)

In addition, the movement of passengers to high-speed has freed up conventional rail. Rail operators are taking advantage of this by increasing the commercial traffic on those lines.

After 2003, the government investments in rail, both high-speed and conventional, surpassed those dedicated to roads; they recently reached more than $6 billion a year, approximately 0.6 percent of the Spanish GDP.

Trains

The rapid growth of high-speed rail in Spain has encouraged Spanish companies not only to create products that meet the demands of the Spanish market but to innovate in ways that allow these companies to compete on an international market as well.

In the early stages of the AVE in Spain, without strong home-grown high-speed rail technology available, French and then later German technology provided the mechanisms to reach the necessary speeds. But the clear and growing market for high-speeds trains within the country provided the motivating factor for two veteran Spanish rail companies, Talgo and CAF, to develop those trains.

Talgo began as a rail company in 1942, when a Spanish engineer tested a new system for axles to avoid wear and tear on train wheels. In the following decades, Talgo provided trains for a variety of specific Spanish needs. In the late 1970s and early 1980s, Talgo engineers developed trains that reached then high speeds of 200 kilometers per hour. Talgo began providing high-quality, inexpensive high-speed trains in the early 1990s.

"In 1988 we came to the conclusion that we had to prepare ourselves for the growth of high-speed rail in Spain and in general in Europe," said José Luis López Gómez, technology director for Talgo. So the company tested a new train on a testing bench in Germany and reached the record-breaking speed of 500 kilometers per hour, though this speed is not yet feasible in the real world because of physical and signaling constraints.

CAF was founded in 1917, providing parts and trams for Spanish lines, including the first metro in Madrid. The company formed an R&D department in 1969. "That to me is the most important date in the company," says a spokesperson for CAF, "because that's when we began to develop our own products."

A Spanish disadvantage—mountainous terrain and frequently curving tracks—led to one Spanish innovation. Because of centrifugal force, as trains travel around curves, the speed pushes the train—and therefore the cars and the passengers within—to the outside of the curve, something that is known to cause passengers a fair amount of discomfort. This effect could also force trains off the rails. To avoid both results, trains often slow down at curves.

Both CAF and Talgo have developed proprietary technology in something called "tilting" trains. Tilting technology detects where and when the track curves, and the train then realigns the suspension through a variety of systems and equipment so the train actually tilts into the center of the curve. This allows even conventional trains from both companies to travel at higher speeds through the curves.

Another particularly Spanish disadvantage has also paved the way for innovation. In the mid to late 1800s, when Spain was first developing its rail network, the country made a deliberate decision to use a gauge, or rail width, different from most of the rest of Europe. The Spanish gauge is 1668 millimeters wide, while the European norm is 1435 millimeters—a difference of more than 200 millimeters. Some experts say this different standard may have been adopted because of concerns over the possibility of invasions from neighboring countries; others say that at the time people believed a wider rail would work better with steam engines. Though the exact reason remains unknown, Spain was left with a major challenge in the development of cross-border travel and trade. Until recently, any train that wanted to cross from Spain to France had to stop, the wheels had to be totally reorganized, and the front car and engine had to be changed.

Talgo developed an automatic gauge-switching system that works in the following way. The train slows down to about 15 kilometers per hour when it reaches the switching station, which contains the original track and the new gauge alongside. At the station, there are lateral guides alongside the track. When the train encounters these guides, its weight transfers, freeing up the wheels and unlocking the bolts that hold the wheel system in place. The wheels automatically move to the newer gauge, and the locks set once again, transferring the weight back to the wheels and off the guides.

CAF trains also operate with a proprietary system developed along the same principles. The guides take the

A Spanish high-speed train waits in the Madrid station.

weight of the train and unlock the wheels. As the train slides along the guides, loosening the axles within the system, the wheels readjust to the new gauge and are locked into place; then the train once again picks up speed.

In both systems, a gauge change—which in the past took up to an hour—takes only about four seconds. Talgo has been operating gauge-switching trains between Barcelona and Geneva since 1968 and between Madrid and Paris since 1980.

Today, the issue of changing gauges along a rail line is about more than frontiers. Spain made the decision to have all new rail lines, the high-speed lines, built at the European gauge width to facilitate movement between countries. Within Spain today, high-speed lines at European widths meet conventional lines at Spanish widths. CAF is operating trains along the Madrid-Barcelona line that change gauges without stopping.

Not only does this new technology allow Spain to easily move people and goods beyond Spanish borders, but it is opening up a new market to CAF and Talgo beyond the borders as well. Though most countries in Europe built trains to the European gauge standard, some countries in the former Soviet Union have a gauge wider than the norm. Talgo tested this system at the borders between Sweden, Finland, and Russia. China and Japan have also expressed interest in the mechanism.

CAF and Talgo are both supplying trains to the Spanish high-speed rail market, and CAF has recently sold the first high-speed rails out of Spain for the new line between Istanbul and Ankara in Turkey.

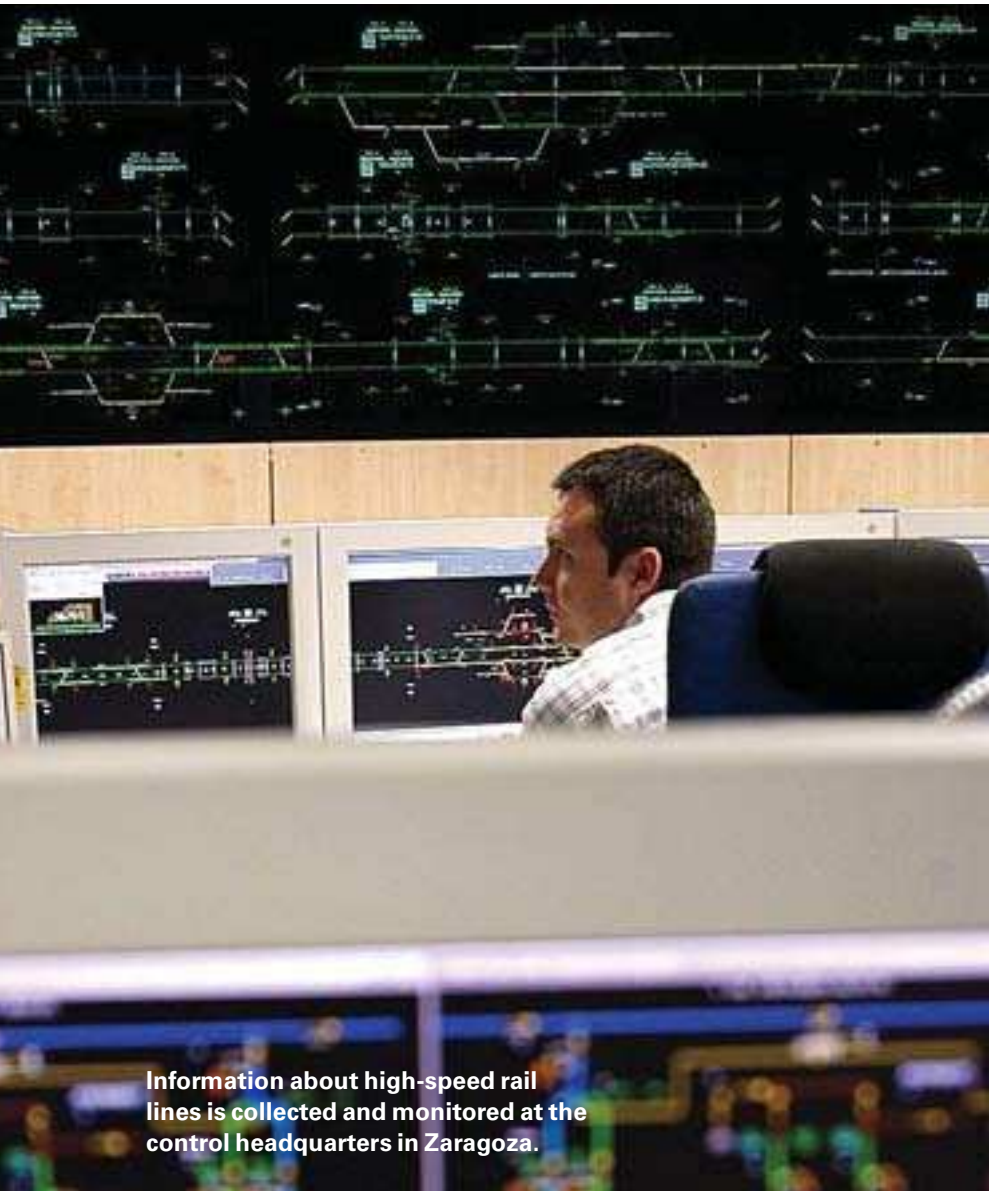
Control Headquarters

In Zaragoza, midway on the journey from Madrid to Barcelona, one room's walls are lined with large panels that glow red, green, and blue against a black background. Marks representing trains blip as they move along luminescent tracks, their position constantly updated as they speed along real-world tracks many miles away. "We have a geographical view of the entire system, all the trains, as if we were seeing the whole system operating in real time," says Javier Rivilla, project manager at Indra.

This is the control center for the entire AVE system, a complicated network of track sensors, signaling technology, radio transmitters, and computer systems that integrates every possible bit of information about the trains and the rail system and updates all that information either in real time or within a few seconds. Its developers like to boast that this system is among the most advanced in the world. "We're in charge here of making sure that everything functions perfectly," says Rivilla.

The company that synthesizes all the information is Indra, one of the top Spanish information systems companies and a top provider of defense contracts in that field. Internationally, Indra is also particularly well known for its air traffic control systems. "Of every five flights in the world, three are controlled by Indra," says Rivilla.

Indra engineers developed the new system starting in 2001 as a partnership with ADIF, while ADIF, searching for a more advanced method of traffic control and information flow, took advantage of the Spanish company's history of innovation in the development of information systems. The new system, called DaVinci, began operations in 2003. With more than four mil-



Information about high-speed rail lines is collected and monitored at the control headquarters in Zaragoza.

lion lines of code, the system integrates all relevant information into a unified platform and automates all tasks related to the technical structure of the system, so the operator can focus on traffic flow.

High-speed rail, like air traffic, demands high-precision information gathering and transmission. Not only does the control center collect data on exactly where each train is at any given moment, but other types of information prove crucial to the functioning of the entire system, such as data from detectors that test the temperatures of the brake boxes so as to avoid overheating and thus a brake failure. The system also collects information on the electricity demand in any part of the line. In addition, fiber-optic sensor systems detect even small fallen objects along rail paths and then sound an alarm to avoid harm.

Of course, throughout the years of high-speed rail around the world, any control system has needed to be able to identify fallen objects, to detect the position of the trains, to determine whether the trains are functioning as they should. In the past, however, each piece of information was determined, received, and transmitted by a separate system. For instance, if a train had to change rails because of a problem along a track, the operator had to contact all other operators in charge of related systems, such as the operator of that particular station. "What ADIF wanted was for someone in charge at the moment to be able to make a few clicks on a keyboard, change the path of the train, and everyone would immediately be notified, with all relevant changes in the system automatically updated," says Rivilla.

All those systems have been totally integrated, which operators say is the particular strength of the Indra system. There are also redundant systems built in, in case one fails. Indra has taken advantage of technological advances in sensors and has developed proprietary information systems, coordinating the entire system on the Internet to provide maximum ease of use.

For the future, newer, more accurate signaling systems will allow higher train speeds along high-speed rail tracks. This will increase the productivity of the entire rail system, but it will also demand increasingly precise data and transmission of that data. Says Rivilla, "As we begin to increase rail speed, I believe we will keep on innovating and advancing within this system, making everything even easier to coordinate and even more automatic."

Signaling

Signaling presents one of the greatest challenges both to the speeds trains can reach and to the interoperability of high-speed rail across the entire European network. Trains traveling at such high speeds demand at least 8 kilometers to brake, and 12 kilometers to brake comfortably and not alarm passengers—something impossible with, for example, road signals such as traffic lights. "These signaling installations have to be designed in such a way that if you have a problem in one site, the system has to know at each moment where the rest of the trains are and get the information to all the trains, allowing them time to slow down and prevent a collision," says David Sanz García, account manager for sales and marketing at Dimetronic, a Spanish signaling company.

Each country, though, has devel-

oped its own technology, its own signaling systems. This has presented a challenge to the interoperability of the European high-speed rail network. Trains crossing borders needed to be equipped with a variety of technologies to read the different types of signals. To deal with this, in the early 1990s the European Union demanded a standardized system called ERTMS. It works by standardizing both the information and the means of transmission that trains automatically send and receive to and from signaling control systems, so as to obviate the need to change systems upon changing countries.

This new signaling system was developed to be open and available for the use and integration of any number of companies around Europe; any company could develop a system that would meet the specific European standards.

"It's as if in 1990 there were no cars," says Sanz. "So the government comes and says that we have to have a transportation system for everyone that works in all countries, and then goes and tells the industry to make cars. So let's say each company, Volvo or Fiat or any of the others, each has its own car, but each one is capable of traveling on all the roads."

From the beginning, the Spanish government, working in conjunction with top Spanish companies, decided to be a pioneer in the establishment of this system, utilizing it for the construction of all the high-speed rail lines in the country.

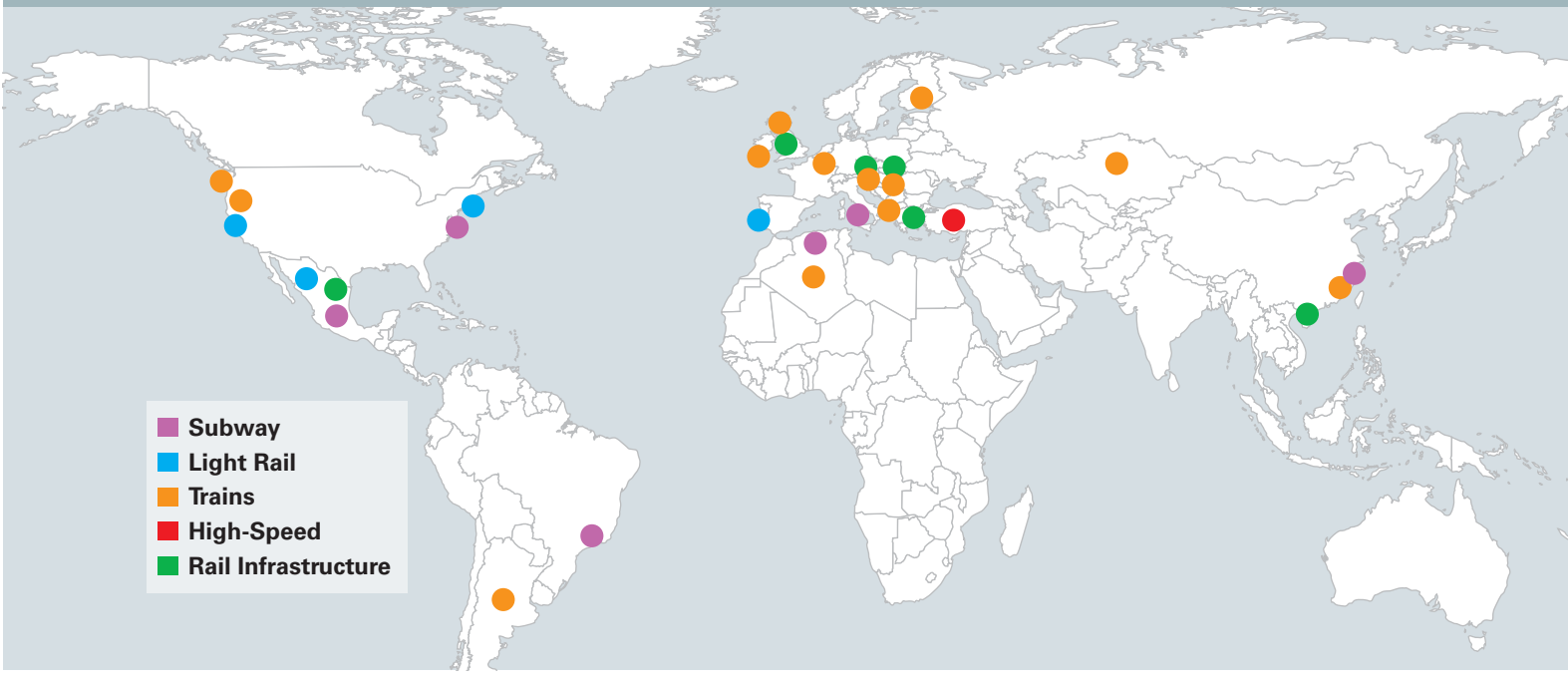
So far, there are three levels of ERTMS; two are available and one is under development. In the first, a system of devices collects all the track information, such as location of trains, and centralizes it in a computer. The information is relayed back to trains by pieces of equipment along the track, which are called balises.

Every element of this system has been specified and standardized. The accuracy of this system allows trains to reach speeds of 250 to 300 kilometers per hour. Level 1 of ERTMS was installed in Spain for first use in a pilot program in 2002 and is being used for all new high-speed lines built since.

ERTMS Level 2 uses less rail-side equipment and provides a higher level of accuracy, thus both allowing trains to run at increased speeds and allowing an increased density of trains running on a given track. Instead of using balises—discrete information delivery—Level 2 sends information continuously through a standardized radio system called GSM-R, using electronic safety equipment called radio block centers (RBCs). ERTMS 2 is in the final testing phase and will be commissioned by Dimetronic by the end of 2006 for the high-speed line between Madrid and Málaga in the south. Level 3 is under development and will allow even higher speeds and train densities on the tracks.

Dimetronic has taken the lead in Spain in developing a system to meet these needs. The system contains two main parts. One consists of the hardware: the balises and the electronic units that process the information that the balises relate to the trains, and the RBCs. The other is the system of software, programming each element and all the messages that will be transmitted. This, however, is similar to what all other signaling companies are designing around Europe. "As ERTMS is standardized, there are more subtle ways for companies to distinguish themselves from one another," says Sanz, "such as the reliability of the

Sample of International Spanish Rail Projects



system and its general performance." Dimetronic has designed peripheral equipment and subsystems of the signaling system that make it competitive on the international market.

The design of a testing system has made the biggest difference in the Dimetronic technology. This complex computer system allows engineers to input all the relevant data and ensure that all testing can take place in a laboratory, avoiding long real-time trials and resulting delays in the system's use. Says Sanz, "This system is something that no other company has. It's not the core of ERTMS, but it's a related product that adds value and allows the client to put the product into service that much more quickly."

Building the Rails

Pig iron and steel shine incandescent orange at the Aceralia mills in northern Spain, owned by the Arcelor-Mittal group. The furnaces and mills at the sprawling site have churned out more than 400,000 tons of high-speed rail for use in countries including Spain, Portugal, France, and Germany, making this site one of the largest rail producers in the world.

The points at which individual rails are soldered together create a weakness in the rail. Railways for high-speed trains must be longer than 270 meters after electric welding in order to lessen this effect. Arcelor Rail developed the facilities for high-speed rail in 1990—a kilometer-and-a-half-length building filled with the clangs and heat of metal production. In a building this size, Arcelor is able to provide 90-meter-long rails, significantly longer than rails needed for conventional tracks. "With a longer rail, the security of the rail is higher because of the avoided soldering points," says Fernando Sáinz-Varona, rail marketing and controller manager. "And the cost is lower, as welding also adds to the cost of the rail."

High-speed rail demands that metal meet very exacting standards. The quality and homogeneity of the material must meet a strict standard and be developed with specific temperature and chemical requirements. This avoids, for example, an imperfection that could lead to a stress fracture in the rail.

To maintain these standards, Arcelor has created an ultrasonic testing system so particular to this type of material, and so proprietary, that no photos of the equipment are allowed. A physical sensor tests external surfaces for even the most minor imperfections, and ultrasound waves measure the internal quality of the material. "For high-speed rail, everything has to be perfect, both inside and outside," says Sáinz-Varona.

In addition, Spanish construction companies, with years of experience designing and building the necessary infrastructure for rail, are now taking their expertise overseas in countries such as the U.K., Mexico, and China.

Speeding Ahead

As the Spanish government continues to rapidly implement plans to upgrade existing rail lines and build new high-speed rail lines around the country, more and more Spaniards flock to take advantage of the increased flexibility and mobility. Half of the $252 billion budget for the 2005–2020 Transportation Infrastructure Plan is dedicated to rail. According to government estimates (based on the economic value of added jobs, increased mobility, saved time, and decreased pollution and carbon dioxide emissions), rail in Spain contributed to the Spanish government more than three times the amount it received in subsidies.

"We're extremely proud of where we are," says Jiménez of ADIF. "We started with a rail system that was not very competitive, had deteriorated a great deal, was very old—and was even shutting down. Within a short period of time, all that changed. And we've also reached a very competitive technological level, with companies providing equipment, components, civil works, and construction that compete on the international market. All of this makes us very proud of the Spanish model."

Resources

ICEX (Spanish Institute for Foreign Trade)
www.us.spainbusiness.com

Aceralia
www.aceralia.es

ADIF
www.infraestructuras-ferroviarias.com/

CAF
www.caf.es

Dimetronic
www.dimetronic.es

Indra
www.indra.es

MAFEX
www.mafex.es

RENFE Operadora
www.renfe.es

Talgo
www.talgo.com

To find out more about new technologies in Spain, visit:
www.technologyreview.com/spain/train

For more information visit:
www.us.spainbusiness.com

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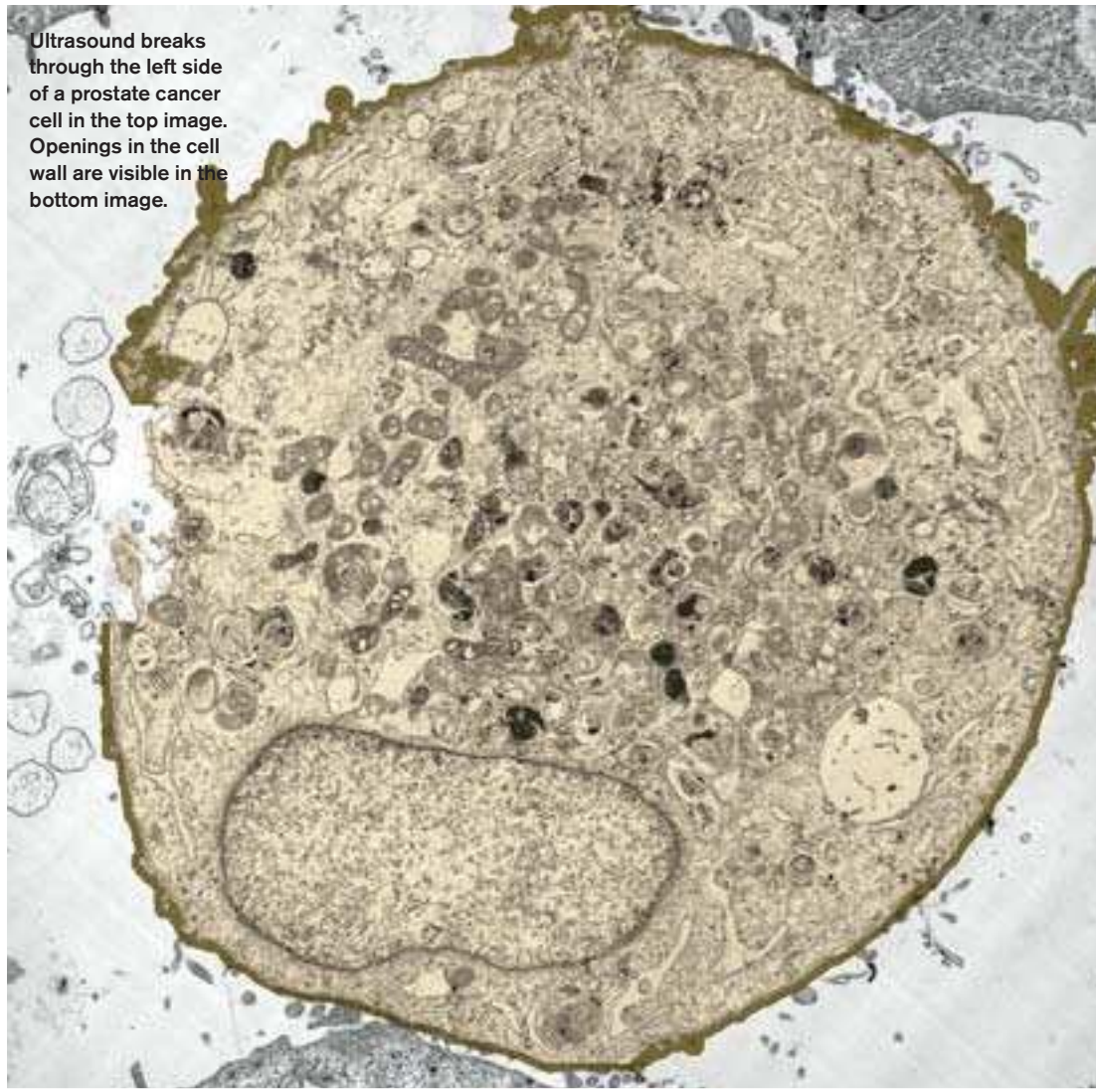
Forward

MEDICINE

Cell Burst

How ultrasound slips drugs into cells

Someday, your doctor may try to rip holes in your cells to get drugs inside. Scientists have long known that ultrasound (at lower frequencies than the ones used for medical imaging) helps get drugs inside cells, but these photos, of prostate cancer cells, are the first to show the process in action. Using several types of microscopy, researchers from the Georgia Institute of Technology showed that ultrasound waves punched holes in the cells' membranes. The pressure of the ultrasound creates tiny bubbles, says Mark Prausnitz, the professor in the School of Chemical and Biomolecular Engineering who led the work. When the bubbles burst, a wave of fluid movement opens up a small breach. The damage is temporary: researchers found that within minutes, the cells could manufacture and dispatch tiny spheres of membrane material that would patch the holes.



Ultrasound breaks through the left side of a prostate cancer cell in the top image. Openings in the cell wall are visible in the bottom image.

ROBYN SCHLICHER, ROBERT APKARIAN, AND MARK BARAN

The ultrasound technique could become a way to target delivery of gene therapy or chemotherapy to specific tissues, or to transport large-molecule drugs that can't otherwise pass through cell membranes. Ultrasound wands could be pressed against the skin, with their energy focused on specific internal tissues. Safety studies are likely to take several years, says Prausnitz, but if all goes well, this could become an approved procedure in five to ten years. **EMILY SINGER**

ENERGY

Window Power

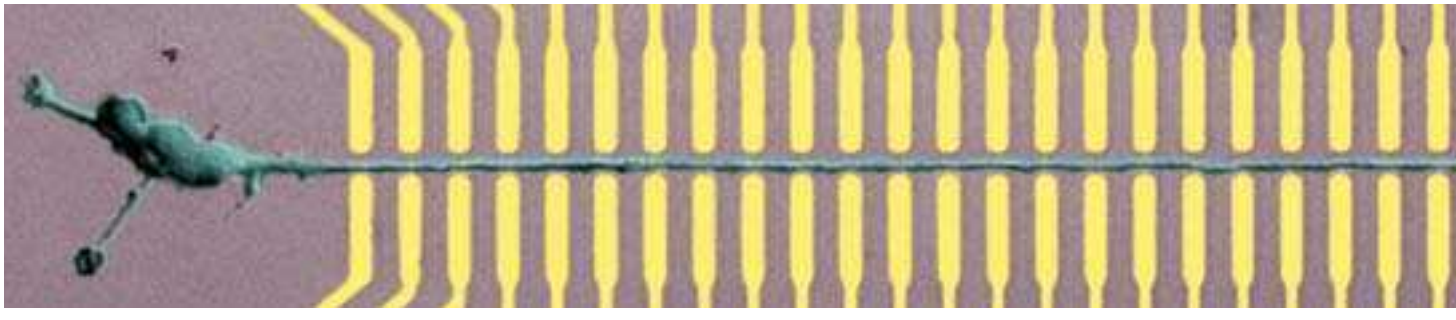
The next building material to generate solar power may be windows. In a dye-sensitized solar cell, dye molecules attached to nanoscale titania particles are held between two panes of glass; the dye absorbs light and releases electrons, which are harvested by the titania. The basic concept was invented 15 years ago by Michaël Grätzel, chemistry professor at the École Polytechnique Fédérale de Lausanne in Switzerland. Now, the technology is in limited production by Konarka, a company based in Lowell, MA, and will soon be more widely available. "The normal configuration has glass on both sides and can be made to look like a colored glass," Grätzel says. "This could be used as a power-producing window or skylights or building facades. The wall or window itself is photovoltaically active." This could give a whole new meaning to the term "power windows." KEVIN BULLIS

Bars on a solar cell's surface collect current. The light-absorbing dyes inside the cell can be of various decorative colors.

NANOTECH

Neuron on a Chip

Tiny changes in the way electrical signals move through neurons are the basis of learning and memory—and of many brain pathologies. But it has been difficult for neuroscientists to observe these changes in much detail. Now, researchers at Harvard University have created a tool with unmatched sensitivity: silicon nanowires that amplify very small electrical signals from as many as 50 places on a single neuron. Existing methods can pick up signals from only one or two places. Chemist Charles Lieber and coworkers assemble nanowires on a silicon chip, deposit electrical leads that connect to them, and add protein molecules that promote and control neuron growth. Finally, they seed the chip with rat neurons and wait four to ten days for them to grow. The proteins provide a path for the neuron's growth along the chip, ensuring that it makes contact with the nanowires. The technology could eventually help brain scientists understand the underpinnings of learning, memory, and disease. KATHERINE BOURZAC



Fifty nanoscale devices on a chip measure electrical signals traveling along a single neuron.

COURTESY OF WINFRIED HOFFMANN (WINDOW); LIEBER GROUP, HARVARD (NEURON)

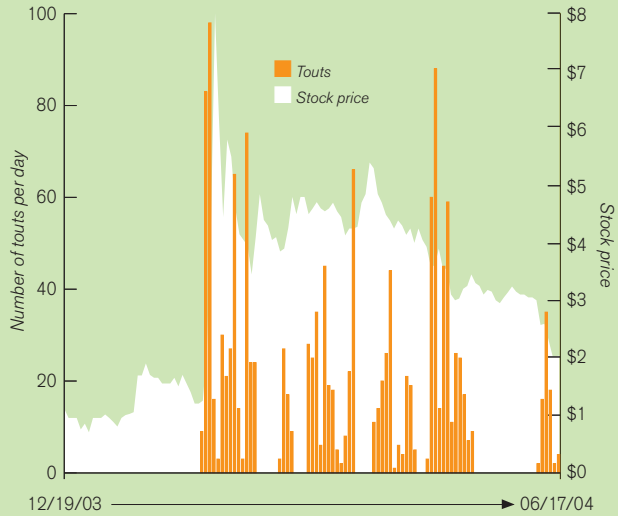
INTERNET

The Value of Spam

A recent study says that sending out stock-touting spam can be highly profitable. An analysis of more than 75,000 spam stock touts received by an e-mail account and a Usenet newsgroup between January 2004 and July 2005 showed that they were often followed by increases in trading volume, creating the liquidity necessary for the spammers to dump their shares. If a spammer bought a stock a day before heavy touting, then sold it the next morning, he or she took profits averaging 4.9 percent. Some spammers saw returns as high as 6 percent. One of the study's authors, Jonathan Zittrain, professor of Internet governance at the University of Oxford and a visiting professor at Harvard Law School, says one countermeasure could be for brokerage houses to impose waiting periods between trades on first-time penny-stock investors, as is done with some options trading. **TYLER HAMILTON**

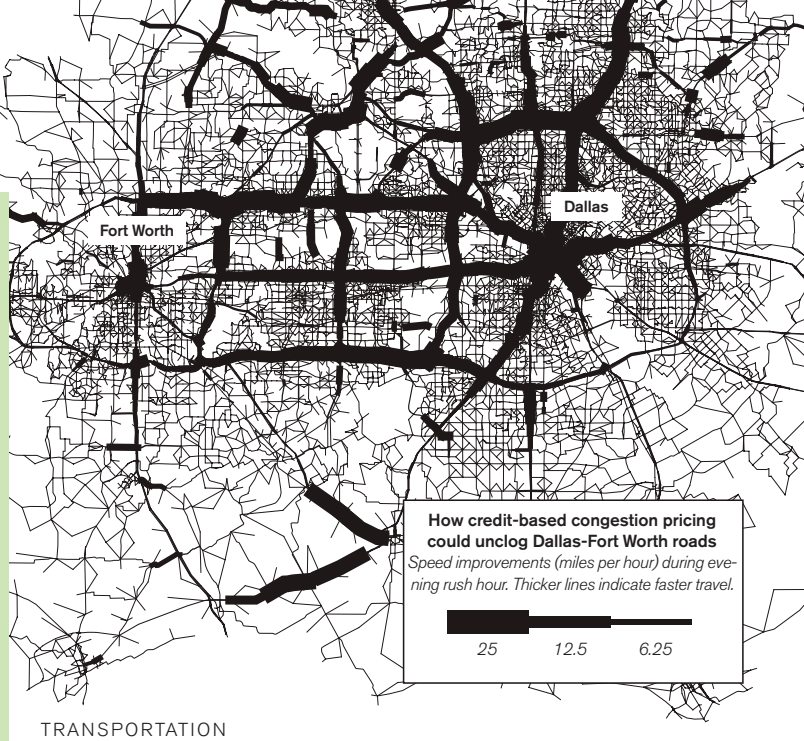
The Spam Effect

Daily spam-tout activity for penny stock China World Trade is compared with share price over a six-month period.



Source: Laura Frieder and Jonathan Zittrain, "Spam Works: Evidence from Stock Touts."

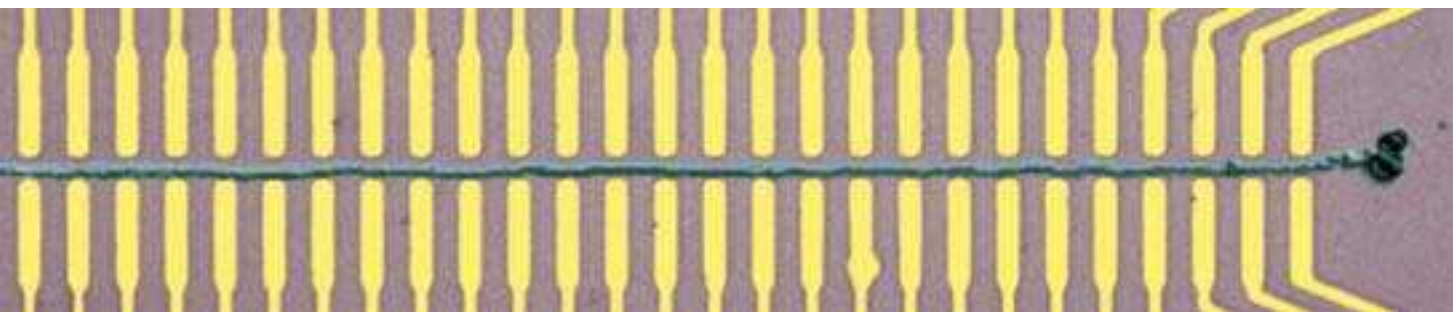
COURTESY OF KARA KOCKELMAN AND PRADEEP GULIPALLI (CONGESTION)



TRANSPORTATION

Congestion Control

New research shows we don't need new roads to reduce traffic in metropolitan regions—just creative tolls. The results above show how traffic speeds would improve on the highway network around Dallas and Fort Worth, TX, under a scheme of "credit-based congestion pricing," according to Kara Kockelman, a civil engineer at the University of Texas at Austin. Vehicles would be monitored with radio frequency identification (RFID) or GPS technologies that would track where and when they were driven. Drivers would get a fixed monthly allotment of credits, which they'd "spend" on tolls that would vary according to mileage and location. Tolls would be as high as 20 cents per mile, for bottleneck stretches at peak times, but drivers would pay real money only if they'd used up their credits. The benefit: traffic up to 25 miles per hour faster during rush hour. At least, that's what Kockelman's computer model concludes after analyzing such factors as trip frequency and the value drivers place on saving time. The idea is under study; implementation would take years and would have to address privacy concerns. **DAVID TALBOT**



TRANSPORTATION

BMW: Engine for Hydrogen

If hydrogen fails as a transportation fuel, nobody can blame BMW, which has built prototype hydrogen-gasoline internal-combustion engines for years and is now touting a version *(above)* that's undergone rigorous product development. BMW plans to give 100 luxury hydrogen cars next year to politicians, celebrities, and other people who can promote hydrogen. The engine can generate 260 horsepower, something a full-size electric car powered by a hydrogen fuel cell cannot now do, says Thomas Korn, senior project engineer for BMW's hydrogen program in Oxnard, CA. Although hydrogen combustion leads to the formation of nitrogen oxides, BMW's new car has sophisticated control systems that minimize those pollutants by optimizing hydrogen concentrations and engine timing. But will it ever make it to the mass market? It's a long shot, says John Heywood, director of the Sloan Automotive Laboratory at MIT. Despite the need for cleaner cars, he says, "a feeling is growing that, really, hydrogen isn't a particularly convenient way of doing all of this."

DAVID TALBOT

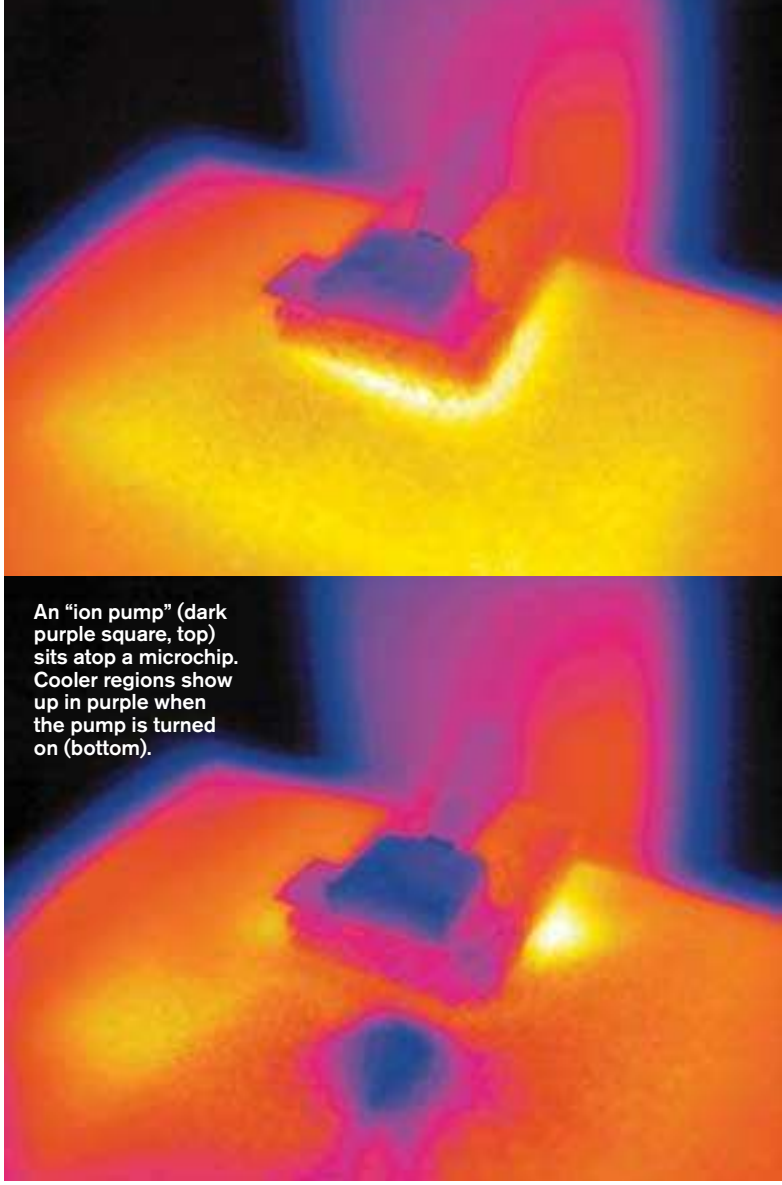
SPACE

Staring at the Sun

Solar eruptions scatter high-energy magnetic particles throughout the solar system and can disrupt Earth-orbiting satellites, wreaking havoc on TV transmissions and communications. This fall, NASA plans to launch two satellites that will help astronomers better predict these gigantic events. The satellites, loaded with instruments such as 3-D imagers and particle and magnetic-field detectors, will track Earth's orbit around the Sun, with one ahead of and the other trailing Earth. Their readings will be combined into a stereo-like view that will enable earlier warnings of solar activity, allowing satellites to power down or go on standby. "It's like turning off the TV during a lightning storm," says Michael L. Kaiser, a NASA scientist on the project.

An artist's rendering depicts Sun-watching satellites.

KATHERINE BOURZAC



An "ion pump" (dark purple square, top) sits atop a microchip. Cooler regions show up in purple when the pump is turned on (bottom).

HARDWARE

Self-Cooling Microchips

As computer chips are crammed with more and more transistors, they run hotter, and traditional cooling mechanisms—heat sinks and fans—are having trouble keeping up. But future chips might cool themselves with a special gadget that uses ionized air and an electric field to create a tiny breeze. In a so-called ion pump, a high voltage across two electrodes strips electrons from molecules of oxygen and nitrogen in the air, creating positively charged ions. These ions flow to the negatively charged electrode, dragging along surrounding air molecules and cooling the chip. Researchers from Intel, the University of Washington Seattle, and Kronos Advanced Technologies of Redmond, WA, say a prototype can cool a two-square-millimeter spot on a surface by 25 °C. Since the ion pump is made from silicon, it can be constructed as part of the chip-making process. Project leader Alex Mamishev, an electrical engineer at the University of Washington, says he expects the technology to be incorporated into commercial chips within two years. KATE GREENE

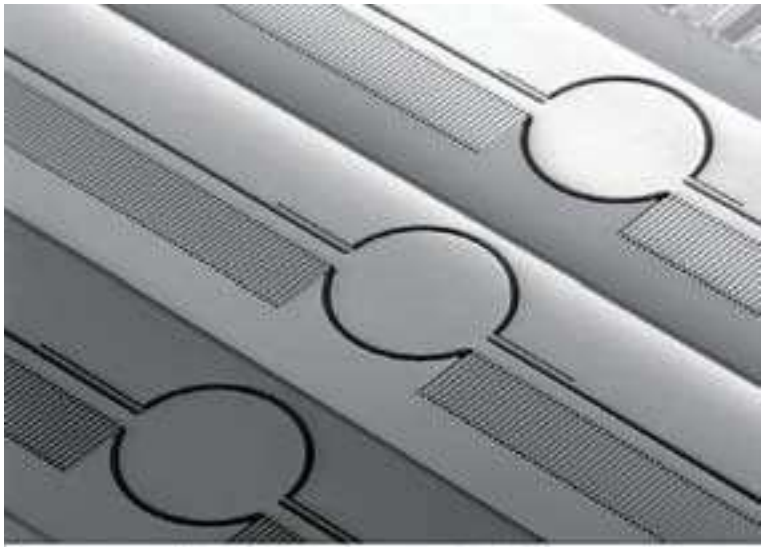
COURTESY OF BMW (ENGINE); COURTESY OF NASA (SUN); NELS JEWELL-LARSEN, UNIVERSITY OF WASHINGTON (MICROCHIPS)

INTELLECTUAL PROPERTY

Patent Objector

The U.S. Patent and Trademark Office too often grants patents that are overly broad or cover well-established common practices—thwarting innovation and imposing high costs on would-be competitors. So says Dan Ravicher, founder of the New York City–based Public Patent Foundation, who challenges patents by asking the patent office to narrow claims. Here's where three of his highest-profile fights of 2006 stand. **ELI KINTISCH**

Patent	Ravicher's peeve	Update
Embryonic stem cells Wisconsin Alumni Research Foundation (WARF), Madison, WI	WARF charges high royalties to biomedical companies.	In October, the patent office agreed to reëxamine the patents.
Data compression method Forgent Networks, Austin, TX	Forgent is suing major software companies for substantial royalties for using the JPEG photo standard.	In May, the patent office rejected 19 of the patent's 46 claims.
File sharing between different operating systems Microsoft, Redmond, WA	The patent makes it difficult for alternative operating systems to work with Windows.	In January, the patent office let an altered version of the patent stand.



Circular mirrors carved into silicon are controlled by motions of comb-shaped structures.

MATERIALS

Guiding Eye for MEMS

Problem: To make sure they target the right parts of the cornea during vision-correcting Lasik surgery, doctors rely on a scanner that responds to eye movements and redirects laser pulses. Today's scanners cost thousands of dollars and still offer less than ideal precision.

Solution: At the University of California, Berkeley, researchers in the Microfabrication Laboratory used inexpensive techniques to build a microscale scanner that moves up to 30,000 times per second, up from the 4,000 times per second of conventional technology. Graduate students Hyuck Choo and David Garmire invented a way to carve one piece of silicon into two interlocked comblike structures. Applying a voltage to one comb makes the other move up or down. A mirror attached to the combs redirects a laser beam. While "comb drives" are already used in some microelectromechanical systems (MEMS), the combs have had to be built on separate silicon wafers and wedged together manually. Because the new device is easy to manufacture, "this is not just an incremental step but a major development," says Roger T. Howe, the Stanford University electrical engineer who invented the comb drive in the 1980s. Choo says the technology could be cheaply incorporated into surgical scanners and other devices. **WADE ROUSH**

COURTESY OF HYUCK CHOO (MEMS); COURTESY OF GOOGLE (EARTH)

INTERNET

Annotating the Earth

Finding information linked to geographical locations became far easier last year with the launch of Google Earth, a collection of zoomable aerial and satellite photos carpeting a 3-D model of the earth. Now, deeper layers of information are becoming accessible. With the click of a mouse, icons linking to masses of information provided by organizations such as the United Nations, the U.S. National Park Service, National Geographic, and the Discovery Channel appear atop the Google Earth landscape. Depictions of buildings, national boundaries, and road networks have long been part of Google Earth. But the new service is Google's first official attempt to build what might be described as a geographically indexed world encyclopedia. WADE ROUSH

A satellite shot of Egypt's great pyramids now includes an icon leading to documentary videos.

NANOTECH

55,000 Tiny Pens

Researchers have developed a device that uses 55,000 microscopic "pens" to write patterns with nanoscale features—and could even use biological molecules such as DNA or proteins as "ink." The tool could someday lead to powerful new diagnostic tests and cancer therapies. Created by Northwestern University chemist Chad Mirkin, the device is a leap forward from earlier versions that had just one pen *(see "Nanobiotech Makes the Diagnosis," May 2002)*. The greater numbers translate to added speed, which could allow researchers to run thousands of experiments at once. For example, they could print nearly infinite combinations of proteins and test their effects on cells, a process that could lead to new drugs. The new nano machine is fast: as a demonstration, Mirkin printed 55,000 images of a nickel in an area smaller than a dime—and did it in less than half an hour. KEVIN BULLIS

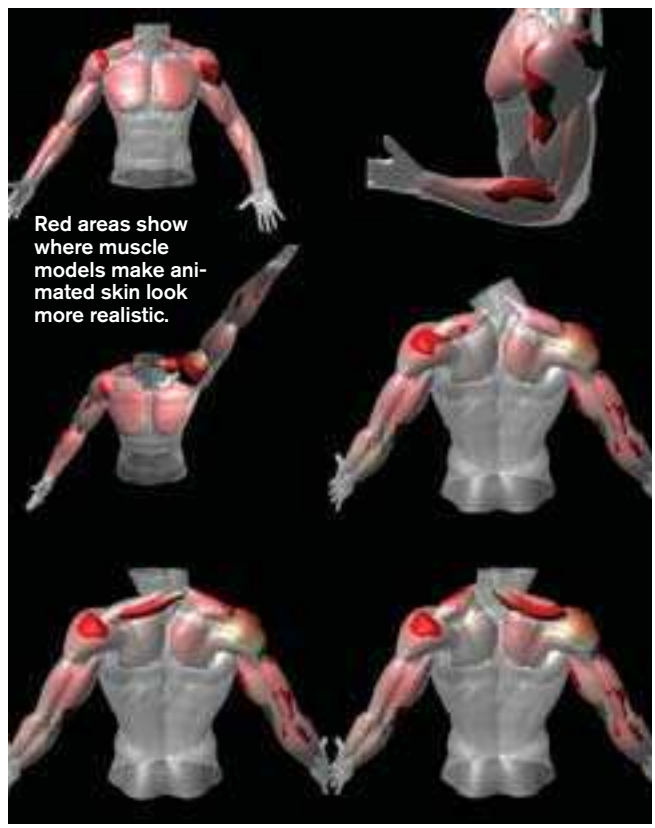
Each pyramid-shaped pen tip is about 20 nanometers wide.

BIOTECH

On Autism's Trail

A new microarray that can simultaneously detect 500,000 or more specific genetic variations, covering almost every gene in the genome, will provide better insights into the complex genetic bases of many illnesses. Using the chip from Santa Clara, CA–based Affymetrix (a similar one is made by San Diego–based Illumina), researchers worldwide are seeking genetic causes of diseases such as autism, diabetes, and Alzheimer's. Below is a sampling of these efforts. EMILY SINGER

Disease	U.S. sufferers	Status
Autism	1 million to 1.5 million	Genetic data from 3,700 people with autism are now being analyzed.
Alzheimer's	4.5 million	Genetic data have been collected from 1,645 Alzheimer's patients. Results from analysis are expected late this year or in early 2007.
Type 1 and type 2 diabetes	20.7 million	Early results from a study of 2,000 sufferers of each diabetes type are expected by early 2007.
Hypertension	65 million	Early results from a study of 2,000 sufferers are expected by early 2007.



Red areas show where muscle models make animated skin look more realistic.

SOFTWARE

Graphic Muscles

If you don't want your animated characters to look fake, you need to work on their muscles. Jian Zhang, professor of computer graphics at Bournemouth University in England, says the key to realism is to build a character's muscles first *(left)*, then add skin. It's counterintuitive for an artist who has a character's external appearance in mind, but it makes for natural-looking movements. An algorithm created by Zhang and colleagues combines the muscle-based model with existing ones based on the movements of skin alone. KATE GREENE

COURTESY OF AFFYMETRIX (AUTISM); CHAD A. MIRKIN, NORTHWESTERN UNIVERSITY/NANOINK, INC. (PENS); XIAOSONG YANG/XIN HE (MUSCLES)

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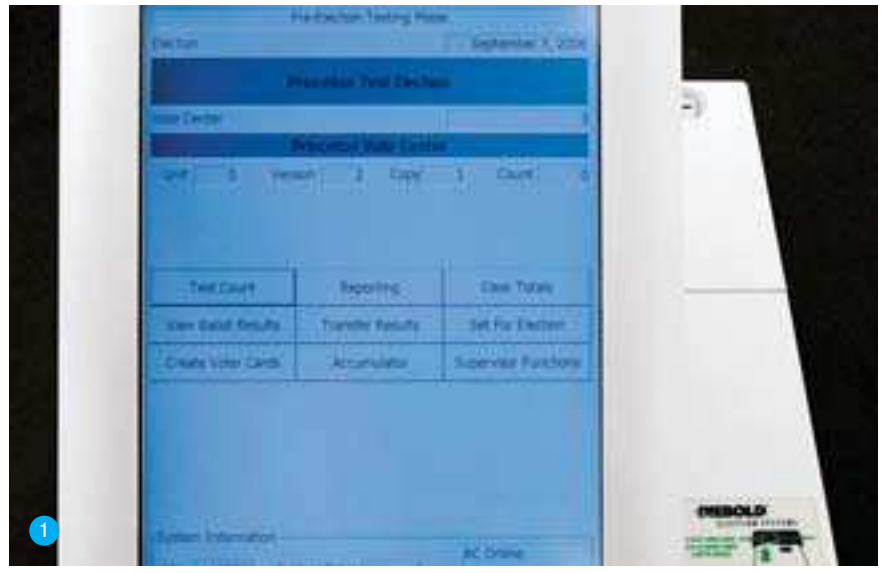
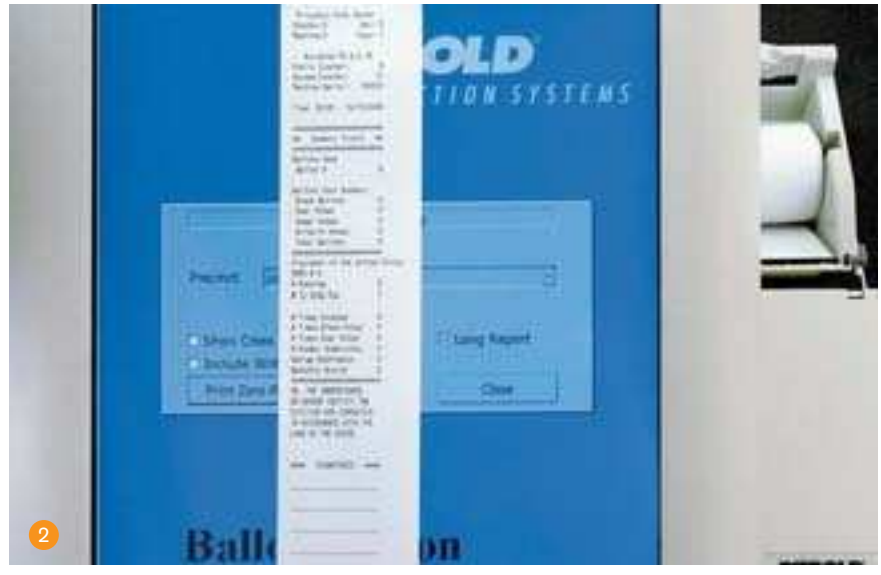
How to Steal an Election

Princeton University computer scientists expose the weakness of a Diebold voting machine.

By Daniel Turner

This September, researchers from Princeton University's Center for Information Technology Policy (CITP), led by Edward Felten, released a damning paper and accompanying video that showed how easily they were able to rig a mock election by loading a virus of their design onto a Diebold AccuVote-TS, one of the most commonly used electronic voting machines in the United States. The CITP received its machine from a third party who remains publicly anonymous. Diebold has responded that those of its machines now in use feature upgraded software that enhances security. To see Diebold's response to the Princeton hack, go to www.diebold.com/dieboldes/pdf/princetonstatement.pdf. To see CITP's counterresponse, go to www.freedom-to-tinker.com/?p=1065.





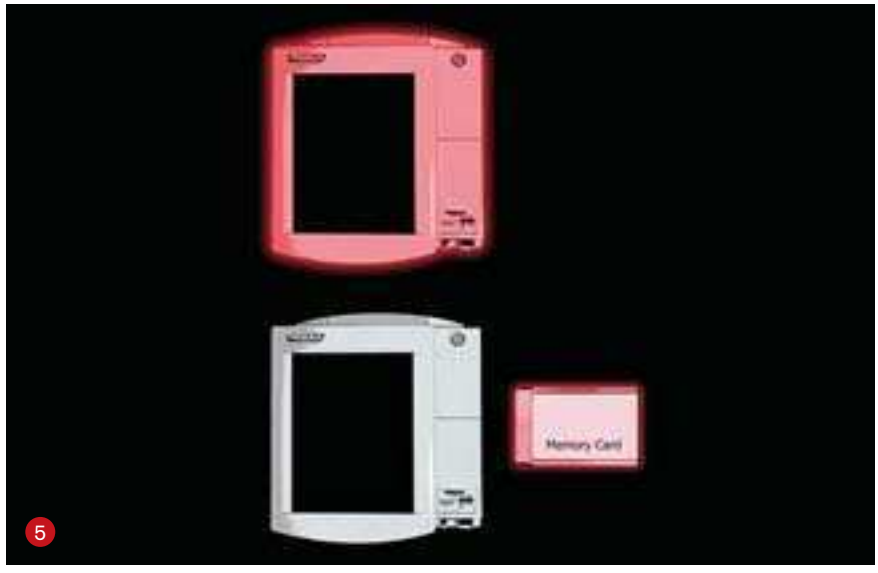
COURTESY OF THE PRINCETON UNIVERSITY CENTER FOR INFORMATION TECHNOLOGY POLICY

1 The Verification Program

Diebold recommends that election workers run a verification program on its voting machines before election time. However, if the virus Felten and his team designed has already made its way onto a machine before it's tested (see "The Virus," opposite), the virus lies dormant, allowing workers to believe the machine is functioning properly. The virus can also delete itself once the election is over, leaving behind no evidence that the machine was tampered with.

2 The Test

Because the virus can tell when an election worker is testing the machine for accuracy, it allows the test vote to register unaltered on the screen and on the machine's internal paper tape. Here, the infected Princeton machine passes the test; in an election, it would be considered reliable.



3 The Break-In

Before a typical election, workers insert a memory card into each AccuVote-TS. The cards have been programmed, at a central location, with the data to be displayed to voters, such as candidates' names. But their chief purpose is to record votes. At the end of an election, the cards are sent back to election headquarters for collation. Each voting machine's memory-card slot is protected by a locked panel. However, the lock is of a standard commercial kind: one Princeton researcher can pick it in seconds. And though Diebold recommends using stick-on security tags on the doors and memory cards, a non-Princeton researcher finds these easy to peel off and reapply, virtually undetectably.

4 The Memory Card

If the researchers insert a memory card containing the virus into the Diebold machine, pressing the power button causes the machine to reboot and automatically install any software on the card. To mute the machine's startup chime, the researchers can simply insert a headphone plug into the machine's audio jack. After the reboot, the researchers can swap back in the original memory card and close the hacked machine's side door.

5 The Virus

Memory cards can spread the malicious software. Once one Diebold machine has been hacked, it will install the virus on its own memory card, as well as on any other card that's inserted into it, such as one being used to distribute a software upgrade.

6 The Results

At the end of an election, each machine prints out its results on a paper tape. In their video demonstration, the Princeton researchers hold an election between George Washington and Benedict Arnold; four votes are cast for the former and one for the latter. Yet thanks to the vote-stealing virus, the Diebold machine's internal memory and internal paper tape show Arnold winning three to two. The election has been stolen.

Danny Hillis

Thinking machine

In 1982, when he was still a student at MIT, Danny Hillis cofounded Thinking Machines, one of the most famous failures in the history of computing. A hive of wayward and brilliant researchers, Thinking Machines tried to build the world's first artificial intelligence. But if the company did not succeed in "building a machine that will be proud of us" (its corporate motto), its Connection Machine demonstrated the practicality of parallel processing, the foundation of modern supercomputing. Today, Danny Hillis is cochair of Applied Minds, a design and invention company, and he is building the Clock of the Long Now, a mechanical timepiece meant to last 10,000 years.

***TR*: Why is creating an artificial intelligence so difficult?**

Hillis: We look to our own minds and watch our patterns of conscious thought, reasoning, planning, and making analogies, and we think, "That's thinking." Actually, it's just the tip of a very deep iceberg. When early AI researchers began, they assumed that hard problems were things like playing chess and passing calculus exams. That stuff turned out to be easy. But the types of thinking that seemed effortless, like recognizing a face or noticing what is important in a story, turned out to be very, very hard.

Why did Thinking Machines fail to create a thinking machine?

Well, the glib answer is that we just didn't have enough time. But enough time would have been decades, maybe lifetimes. It is a hard problem, probably many hard problems, and we don't really know how to solve them. We still have no real scientific answer to "What is a mind?"

The Connection Machine was an effective platform for supercomputing. Why didn't Thinking Machines prosper as a supercomputing company?

Supercomputing turned out to be a technology, not a business. My friend Nathan Myhrvold, who was running Microsoft Research at the time, once told me, "It is at least as hard to make software for a supercomputer as for a PC, but you only have a few thousand customers, and we have billions. Not only that, but each of those customers actually expects you to give them exactly what they need."

What were the successful commercial applications of the research at Thinking Machines?

The commercial applications were mostly chip design, data mining, text search, cryptology, computational chemistry, computer graphics, financial optimization, seismic processing, and fluid flow modeling. Scientific applications like astronomy, climate modeling, or quantum chromodynamics were exciting when they helped get a result on the cover of *Nature*, but we never made money on them.

What happened to the patents from Thinking Machines? More than anyone else, you are responsible for massive parallel processing. You get credit, but no payment. Who gets it, and why?

Well, first of all, I should be clear that I am just one of many people who contributed to developing massively parallel computing. As for the patents, one of the consequences of Thinking Machines' failure is that I lost any rights to the technologies. In retrospect, that turned out to be a blessing, because it saved me from spending the next decade of my life in court.

How is your philosophy of artificial intelligence different from Marvin Minsky's famous "society of mind"?

Marvin is my mentor, so any philosophy of AI that I have starts with his. I was living in his basement while he was writing the book *Society of Mind*, and every day he would write a new page or two and let me read it. Then we would get to talk about it, and I would get to hear all the thought that he had put behind it. I still can't imagine what it would be like to read that book, cover to cover, without a long conversation on each page. But that is the point of the book: as Marvin would put it, "The brain is a kludge." There are a lot of different things going on, and they interact in complicated ways. Marvin is surely wrong on most of the details, but I think the big picture of lots of different, loosely coupled semiautonomous processes is basically right.

You were ahead of your time in applying computation to immunology, genetics, and neurobiology. Today, computation is ubiquitous in biology. What will this mean?

I am excited that computational biology is coming into its own. It feels like the field of computing did in 1970. Everything seems possible, and the only constraint is our imagination. There are still so many basic, simple questions that are unanswered: "How are memories encoded?" "How does the immune system have a sense of 'self'?"

I am especially interested in what will come of computational models of evolution, although I have to admit that the field seems a bit stuck right now. Most current models of evolution reduce it to a very weak kind of search algorithm, but I have always felt that there is something more to it than that. It is not that the biologists are wrong about the mechanisms, but rather that the models are much simpler than the biology. It may be that the interaction of evolution and development is the key, or behavior and environment, or something like that.

JASON PONTIN

DANIEL HENNESSEY

Danny Hillis at the office in an H-1 engine of a Saturn 1B rocket, the first engine stage for *Apollo 7*

INFORMATION TECHNOLOGY

Computer Lesson

Simeon Simeonov thinks special care must be taken when introducing computers to schools in developing countries.

Over the decades, as computers have become less scarce, they have been put to less and less valuable use. (I confess I have caught myself adding three numbers in Excel.) Computers were once used only for the most complex and important tasks, and the hurdle for getting access to one was high. Some *Technology Review* readers can remember the days of punch cards—the careful preparation, the waiting, and the cost of making a mistake. I'm of a later generation, but I grew up under Communism, which wasn't known for its abundance of computing power. I have vivid memories of participating in secondary-school programming competitions in the mid-1980s in Bulgaria, where there weren't enough computers in any given school district to pair machines with students. On the morning of a competition, students would study one or more problems, develop algorithms to solve them, write code on paper, and then painstakingly write down variable traces of the code on sample data. During a lunch break, judges would pore over the mostly incomprehensible algorithms and try to figure out which kids had a chance of getting a program to work. In the afternoon, a select few would then be chosen to use the few available computers.

As this example demonstrates, highly motivated people in computing-starved communities make great use of the first few machines they get. But as more computers arrive, the value per computer goes down significantly, because the know-how needed to put them to good use is scarce. In Bulgarian schools, for example, I saw classrooms where only half the machines were functioning; where teachers didn't know, and didn't want to learn, a thing about computers; where basic educational materials for computer use were lacking. At that time, some Bulgarian educators argued that computers were never going to become useful tools for students. Of course, they were wrong. When the resources became available for more than a couple of hours per person per day, there was a big (and, at the time, surprising) jump in productivity driven not only by the increased presence of computers but also by the changed nature of the interaction between humans and computers. When people could access computers frequently and predictably, they were willing to invest in learning what to do with them, whether it was touch-typing or using software. Today, with the development of the Internet, that kind of jump would be even greater.

I expect these lessons to be "generalizable" to other underserved communities, as well as to philanthropic initiatives such as Nicholas Negroponte's One Laptop per Child *(see "Philanthropy's New Prototype," p. 48)*. The initial focus should be on introducing just a few machines and keeping them in working order. Then, as more computers are brought in, equal effort should be made to train educators and students, as well as to manage the naysayers who'd rather see the money spent elsewhere. When there are enough resources that people can reliably depend on computers in schools, Internet cafés, and homes, the true value of access to computing will become apparent. TR

Simeon Simeonov is a technology partner at Polaris Venture Partners, a venture capital firm based in Waltham, MA.

NANOTECHNOLOGY

New Hope for Optical Signal Processing

Photonic crystals may finally make all-optical signal processing a reality. **Marin Soljačić** explains how.

For decades, researchers developing electronics have had enormous success advancing almost any application that has to do with information processing: following Moore's Law, data density on an electronic chip has doubled every 18 months. Although this exponential growth is likely to continue for a while, inherent physical limitations are expected to prevent it from lasting indefinitely. Some of these limitations are already evident: as electronics in computers are forced to operate at ever higher frequencies, power dissipation and consequent hardware heating are becoming a very serious problem. In nodes of optical telecommunications networks, where data needs to be processed electronically at especially high operational frequencies, the problem is even more significant.

Realizing that electronic signal processing would eventually face a fundamental physical limitation, engineers in the early 1980s explored the possibility of building an optical computer, in which data would be carried by light (photons) instead of by charged carriers (electrons). They didn't have an easy time. True all-optical signal processing requires a way of influ-

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Technology
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Technology Review

encing light with light itself. That is, one has to use materials with optical properties that can be modified by the presence of a light signal; this can be used to influence another light signal, thereby performing an all-optical signal-processing operation. Unfortunately, these effects tend to be extraordinarily weak, so the proposed optical logic elements of the 1980s were too large; they consumed orders of magnitude too much power to be feasible. People started viewing optical signal processing as impractical.

Now, however, with the limits of electronics looming much closer, engineers have begun turning to optics again. Indeed, it's likely that data transport between various components of desktop computers (between different parts of the processor, and between the memory and the processor) will soon be performed optically. As the need grows for physical mechanisms that improve our ability to manipulate light, photonic crystals (which were invented in 1987) have emerged as a promising way to meet it.

Photonic crystals are artificially created nanostructured "metamaterials" whose optical properties vary periodically at the scale of the wavelength of light. Sometimes called "semiconductors for photons," photonic crystals offer unprecedented opportunities for molding the flow of light. For example, they have been used to create all-optical switches that are less than a micrometer in size and an order of magnitude faster than transistors used in commercial electronics. Moreover, photonic-crystal designs have been proposed that could enable nonlinear interaction even between single photons. These materials could thus dramatically change the view that optical interactions are too weak to use for signal processing.

Optical technologies will keep penetrating deeper into electronic designs, and photonic crystals will play a major part in making this possible. Information processing in the near future will thus probably be performed by hybrid electronic and optical designs, with optics taking on an ever more important role. TR

Marin Soljačić is an assistant professor of physics at MIT and a member of this year's TR35.

BIOTECHNOLOGY

The Prize of RNAi

The recently discovered role of small RNAs could mean new drugs and a new understanding of fundamental biology, says **Phillip Sharp**.

Only eight years after their 1998 paper in *Nature* announced the discovery of RNA interference (RNAi), in which double-stranded RNA is used to silence genes, Andrew Fire and Craig Mello awoke in the wee hours of the morning of October 2 to the news that they were the 2006 recipients of the Nobel Prize in Physiology or Medicine. Such a short time between discovery and prize often signifies a finding's importance: it took only nine years for Watson and Crick to win the Nobel for discovering the structure of DNA. The Nobel Assembly's confidence in the importance of RNAi is obvious.

The initial experiment by Fire and Mello, showing that double-stranded RNA injected into worms would silence the gene with the corresponding sequence, was a clarion call to labs around the world, announcing a new method for investigating gene functions. After the initial discovery, other labs showed that small double-stranded RNAs could be used to selectively silence genes in human cells, providing a much-sought-after general approach to exploring the functions of all 21,000 human genes.

Over the past five years, the science of RNAi has advanced research in almost all areas of human biology, including work on cancer, obesity, and autoimmune diseases. Several biotech organizations are developing RNAi-type therapeutics to silence genes that cause diseases: drugs that treat macular degeneration, a leading cause of blindness, and respiratory syncytial virus, a cause of death in premature newborns, are already in clinical trials. Since the technology can in theory silence any gene, it might enable a new category of therapeutics similar in breadth to the class of monoclonal antibodies, which now account for billions of dollars in biotech sales.

RNAi also provoked the startling insight that small RNAs could be a key regulator of gene expression. Indeed, other scientists subsequently discovered that genes encoding small RNAs are common; there are approximately 300 to 500 of them in human cells. These are now called microRNA genes and are known to influence the expression of at least a quarter of all human genes. This is a newly discovered level of molecular control. Alterations in control by microRNAs have now been associated with many diseases, and the subject has only begun to be investigated.

The study of small RNAs is still in its infancy. In fact, this past summer, a family of small RNAs, called piRNAs, was discovered in the germline of vertebrates; it is a new field of science. Textbooks in cell biology are literally being rewritten. TR

Phillip Sharp, MIT Institute Professor and 1993 Nobel laureate, is a cofounder of Alnylam Pharmaceuticals, which is developing drugs based on RNAi. He is also a cofounder of Biogen. This year's Nobel laureate Andrew Fire received his PhD from MIT in 1983, working in Sharp's lab.

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Photo Essay

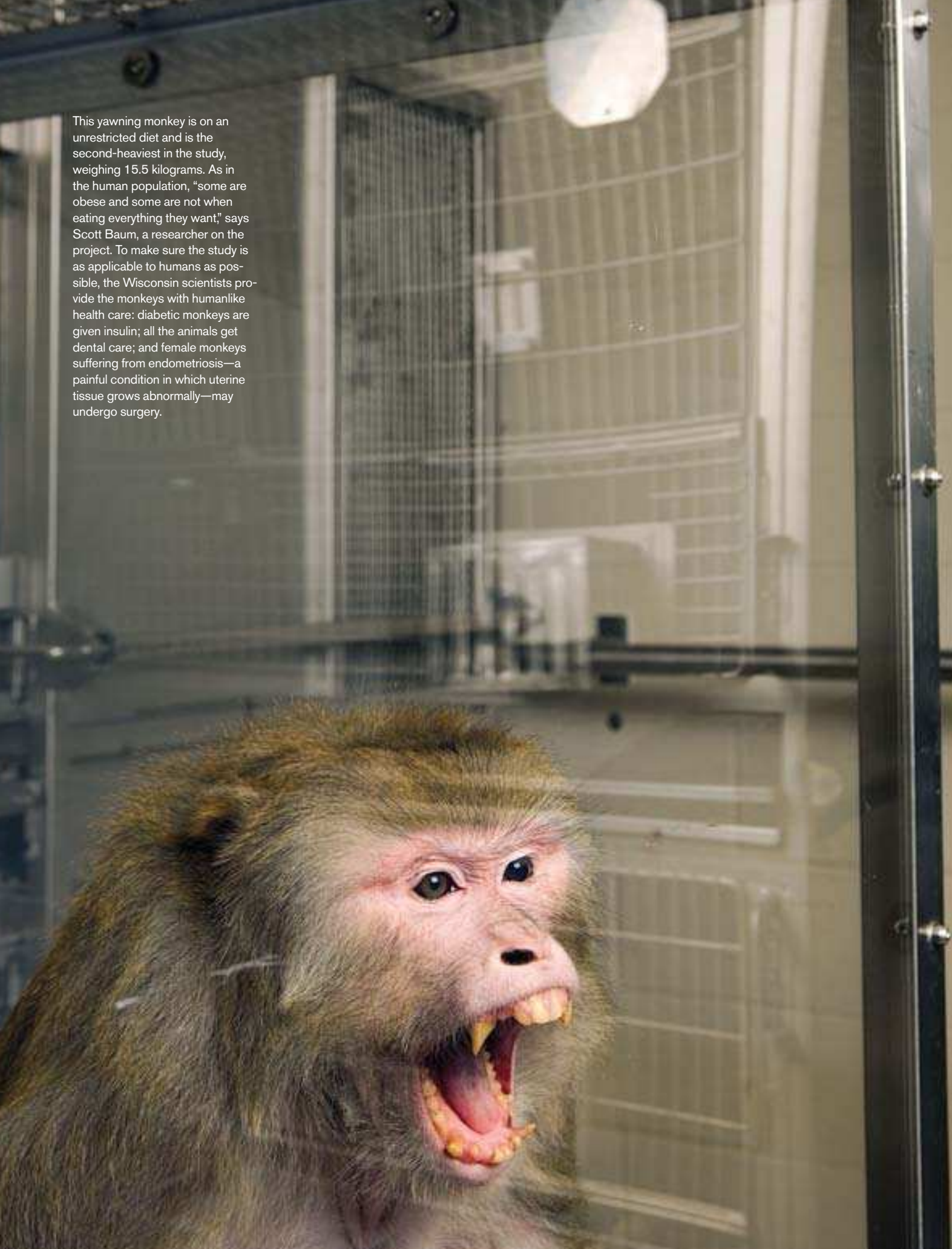
Hungry Monkeys

Scientists know that rats fed a nutritionally adequate diet of 30 percent fewer calories than normal tend to live 30 percent longer. Similar effects have been observed in organisms from yeast to fruit flies but not, as yet, in primates. At the University of Wisconsin, researchers led by Richard Weindruch have been testing a calorie-restricted diet in a group of rhesus monkeys since 1989. The monkey on this page, a dieter, is 25 years old; the one opposite, part of a control group, is a bit over 26. (Both are featured in the next three pages.) Though it's too early to make strong claims about the effects of calorie restriction on these animals, the preliminary results suggest that the dieting monkeys are healthier as they enter old age.

By Katherine Bourzac
Photographs by Kevin Miyazaki/Redux

Of the 76 monkeys in the Wisconsin National Primate Research Center study, which now range in age from 18 to 31 years, 38 are on calorie restriction, including the one in both photos on this page. He weighs 10 kilograms, which is normal for the dieters. The monkey on the opposite page is on a normal diet. The average life span of rhesus monkeys in captivity is about 25 years; Ricki Colman, a scientist on the Wisconsin project, says that 40 years is the known maximum, the equivalent of 120 years for humans. Nine of the animals on normal diets have died of age-related causes such as diabetes and cancer; only five of the dieting monkeys have died of such causes. Colman predicts that it may take another decade to see whether substantial survival differences between the two groups emerge. But there is some evidence that the diet prevents diabetes. Three of the monkeys on an unrestricted diet have the disease, while none of the dieters do. Two monkeys on the restricted diet had early signs of diabetes when they started the regimen, but their symptoms quickly abated.

The orange dumbbell in the cage at left is one of the monkeys' toys.



This yawning monkey is on an unrestricted diet and is the second-heaviest in the study, weighing 15.5 kilograms. As in the human population, "some are obese and some are not when eating everything they want," says Scott Baum, a researcher on the project. To make sure the study is as applicable to humans as possible, the Wisconsin scientists provide the monkeys with humanlike health care: diabetic monkeys are given insulin; all the animals get dental care; and female monkeys suffering from endometriosis—a painful condition in which uterine tissue grows abnormally—may undergo surgery.

The food pellets fed to both groups are almost identical, but monkeys on the restricted diet get a formulation with more vitamins and other nutrients to compensate for the limited quantities. Baum says the animals on the unrestricted diet are given enough food to eat as much as they want. When the monkeys on calorie restriction hear the food cart coming, they run circles in their cages, bark, and squeal; the others are alert but calm. When their trays are filled with pellets, the dieters seem to eat as fast as they can. "They get pretty excited about food," says Joseph Kemnitz, director of the primate center.

Preliminary results from body-composition x-rays like the one shown at right suggest that dieting monkeys may have less age-related loss of muscle mass than the others. They also appear to have less osteoarthritis. The scientists are now beginning gene-expression profiling to test whether the diet prevents age-related changes in gene activity, as it does in mice. The primary goal of the study, director Richard Weindruch says, is to learn, by looking at longevity and disease patterns, whether calorie restriction slows the aging process in monkeys. Researchers hope to discover the molecular mechanisms connecting low-calorie diets to healthy, long life and mimic them with drugs—not necessarily to extend human life, but to make old age healthier by decreasing suffering from cardiovascular disease, dementia, and other age-related maladies.

The Glimmering Promise of Gene Therapy

Its history is marred by failures, false hopes, and even death, but for a number of the most horrendous human diseases, gene therapy still holds the promise of a cure. Now, for the first time, there is reason to believe that it is actually working.

By Horace Freeland Judson

By the late 1960s, molecular biologists had erected an overarching explanation of how genes work—their substance, their structure, their replication, their expression, their regulation or control. Or at least they had done so in outline, for prokaryotes, the simplest single-celled organisms (which include bacteria), and for the viruses, called bacteriophages, that prey upon them. The leaders of the field were now looking to a far more difficult problem: doing it all over again for higher organisms.

What this new generation of molecular biology demanded, and what was developed in just a few years, was a set of methods for investigating and precisely manipulating the genetics of eukaryotes, including animals and plants. With reverse transcriptase, which was discovered independently by Howard Temin and David Baltimore in 1970, genes encoded in RNA could be read back into DNA. With Daniel Nathans's and Hamilton Smith's work on restriction enzymes, segments of DNA could be snipped out at chosen sites. In a rush, from laboratories chiefly at Stanford University, came ways to link together genetic material from disparate sources. "We will be able to combine anything with anything," one senior scientist told me at the time. "We can combine duck with orange." The initial purpose was to get at the most basic questions of cellular biology, to find out exactly what individual genes do and how they do it. Immediately, though, a shining hope dawned: that this toolbox could be carried from the laboratory to the clinic, to cure hereditary diseases caused by genetic defects. Already, some scientists were dreaming of gene therapy.

By 1970, some 1,500 genetically determined diseases had been identified in humans. Some show up in babies; others surface at puberty; a few emerge only toward the end of the victim's reproductive life. Some can be held in check by dietary restrictions, a few by drugs. But most cannot be cured or even palliated by conventional medicine. Though almost all are rare, some extremely rare, collectively they were coming to be recognized as a burdensome and costly medical problem. Many are marked by gross mental impairment. Victims of Lesch-Nyhan disease, for example, suffer severe mental retardation. They must have their arms splinted, because otherwise they bite their hands and arms. They die in childhood or early adulthood. Though scientists had traced fewer than a hundred of these human diseases to specific genetic deficiencies, they began searching for ways to cure them by safely inserting correcting genes into people suffering from them.

They were still trying nearly two decades later, when on September 29, 1999, the front page of the *Washington Post* carried the headline "Teen Dies Undergoing Experimental Gene Therapy." Jesse Gelsinger was 18, a recent high-school graduate from Arizona who had a potentially fatal genetic disease. He was one of 18 patients taking part in a trial at the University of Pennsylvania. Viruses carrying a new gene had been injected into one of the arteries supplying blood to his liver. In gene therapy, an engineered virus is often used as a "vector," delivering the desired gene to the patient's cells; in this case, however, the virus apparently triggered a series of deadly events.

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The *New York Times* picked up the story the day after it ran in the *Post*. The National Institutes of Health and the U.S. Food and Drug Administration started investigations, which moved with commendable speed; more details came out. Later, the U.S. attorney general got involved. But with those first newspaper reports, gene therapy seemed dead.

The trial that Gelsinger had been participating in was tainted by accusations of overconfidence, haste, negligent administration, and conflict of interest. Yet all this diverted attention from acute and fundamental problems with gene therapy itself—problems in the science and technology, problems in clinical exploitation of the technology, problems that were by no means new but that Gelsinger's death made glaringly evident.

I had been following developments in gene therapy for a third of a century, watching as hundreds of millions of dollars were lavished on it, as new hopes cyclically turned to ashes, dramatic claims to sad farce. By 2000, more than 300 gene-therapy trials had been registered with NIH, involving more than 4,000 patients, according to an article printed that year in the Council for Responsible Genetics' magazine *GeneWatch*. The Gelsinger affair was the most highly publicized failure. There had been plenty of others.

There were two chief reasons for pessimism about gene therapy. As had been plain from the start, although the total societal load of illness and debility caused by genetic defects is considerable, most individual diseases caused by single-gene defects—the kind that seem most likely to be cured by gene therapy—are rare. (Sickle-cell anemia and some other hemoglobin disorders are among the few exceptions.) Everybody in the field acknowledged this. Nobody seemed to face up to the implications. Because these diseases have different genetic causes and affect different types of tissue, each presents a new set of research problems to be solved almost from scratch. As the millions burned away, it became clear that even with success, the cost per patient cured would continue to be enormous. And success had shown itself to be always glimmering and shifting just beyond reach, an ignis fatuus: from the start, step by step, everybody had underestimated the real difficulties the science presents.

The history of gene therapy can be told as the repeatedly frustrated search for viruses that work well as envelopes for gene delivery, paralleled by the increasingly baffling realization that far more than a few simple genes are needed to produce the desired proteins successfully. For the gene-therapy community, the years had been a calendar of failures. "We totally underestimated the fact that the viruses could present so many difficulties," Inder Verma—a molecular biologist at the Salk Institute, in La Jolla, CA—told me in August 2006. "We underestimated the fact that it took billions of years for the viruses to learn to live in us—and we were hoping to do it in a five-year grant cycle!" He went on, "You know, the body is designed to fight viral infections. One hundred percent. Luckily for us! And here we are putting billions of viruses back into people and hoping that if we have a good virus, the body will say, 'It's okay, because we're bringing the good stuff.'"

The first attempt at gene therapy in human patients began with a fortuitous observation. In 1959, the physician Stanfield Rogers, at the University of Tennessee, was working with the Shope papilloma virus, which causes warts on the skin of rabbits. He reported in *Nature* that the skin of these warts contained abnormally high levels of arginase, an enzyme that breaks down the amino acid arginine. He then found that some scientists who had worked with Shope virus, even 20 years in the past, had decreased blood levels of arginine.

The possibility that the virus had introduced its gene for arginase into the scientists was a curiosity, nothing more—until 1969, when the *Lancet* published a paper by Heinz-Georg Terheggen, a pediatrician in Cologne, Germany, and colleagues. Two little girls had been brought to Terheggen, deeply mentally retarded and suffering from a form of cerebral palsy, the British journal reported. Tests showed they had high levels of arginine, while very little of the enzyme arginase was detectable. This was a new genetic disease.

Rogers went to Terheggen to urge that he and his colleagues be permitted to inject the girls with Shope virus, hoping to give them a functioning gene for arginase. As an essential precaution, they did try inoculating the virus in a tissue culture of cells from one of the girls. They reported in the *Journal of Experimental Medicine* that they found arginase activity, apparently from the virus-introduced gene. But in the trial, there was no response, no reduction of arginine, no evidence of arginase activity. After an interval, they gave one child a larger dose. Still no response. The general consensus was that Rogers had made a premature attempt, with inadequate scientific understanding. That judgment was not wrong.

In the spring of 1972, Theodore Friedmann and Richard Roblin published the first extended study of the possibility of treating genetic diseases through gene transfer. "Gene Therapy for Human Genetic Disease?" appeared in *Science*. Disease by disease and therapy by therapy, the researchers warned of formidable technical problems; much that they laid out was prescient. They were the first to analyze the potential risks that gene therapy posed to patients and the grave ethical concerns it raised.

Nonetheless, the paper was a work of advocacy. With a medical degree from the University of Pennsylvania, Friedmann had spent three years in the 1960s at NIH, where, in the laboratory of Jay Seegmiller, he had begun to work on Lesch-Nyhan disease. Seegmiller had discovered that the disease is caused by the absence of the enzyme

hypoxanthine phosphoribosyltransferase, or HPRT, owing to a defect in its gene. Friedmann hoped to find a way to put the correct gene into Lesch-Nyhan cells in culture, perhaps using a virus. His imagination had been caught by the prospect of gene transfer. Indeed, as an assistant professor of pediatrics at the University of California, San Diego, in the early 1970s, he introduced the term "gene therapy."

In January 1983, Friedmann and colleagues announced that they had isolated the normal gene for HPRT. Inder Verma, with whom Friedmann had struck up a collaboration in the early 1980s, had a potential viral vector: in this case, a type of retrovirus—one for a mouse leukemia. In August 1983, the two researchers reported that they had built the vector and used it successfully to introduce a functioning gene for human HPRT into rodent cells in vitro.

After that initial glimpse of success, Verma says, "very quickly we asked, 'Can we do it in vivo?'" They began experiments on hemophilia in live mice. The gene defects causing hemophilia were known: the lack of a single protein could prevent blood from clotting. Working in vitro, adding the correct gene to cells in culture, "we could produce the protein forever," Verma says. "And this is where the first surprise came." The moment the cells were put back into the mice, "they instantly stopped making the protein. And this is the first limitation we recognized: retroviruses can only introduce genes when the cells are dividing." Verma adds, "We could take [the cells] out, grow them in vitro, transfuse them with the virus, put them back—but when we put them back, they shut off." Why? "We still really have no idea," he says.

Then, in 1990, an NIH research physician named William French Anderson announced to heated publicity that he was launching a gene-therapy trial, treating two young girls for a form of severe combined immune deficiency, or SCID. People with this disease completely lack a normal immune system. The precursor cells in their bone marrow that should make white blood cells are defective, so patients catch all the infectious diseases that white blood cells should fight off. Mild infections become grave; serious ones kill them. They die in early childhood. Anderson said the two girls were suffering from a form of SCID caused by a lack of the enzyme adenosine deaminase (ADA). He was injecting them with correcting genes carried in murine-leukemia virus.

Anderson was a flamboyantly effective publicist of gene therapy and of himself. He announced that the two little girls had been cured. In September 1994, he brought one of them to testify before the Science Committee of the U.S. House of Representatives. She was eight years old by then, lively and apparently well. The chairman of the committee reportedly called her "living proof that a miracle has occurred." Anderson made sure he was known to the public as "the father of gene therapy," even displaying the title on his website.

Yet his scientific colleagues and competitors became exasperated, even contemptuous. In point of fact, the trial with the two girls had failed. All along, the girls had also been treated with injections of a synthetic ADA. And Verma and Friedmann had already shown the failure of mouse leukemia virus to introduce genes in vivo. "There was never production of the ADA protein—there never was," according to Verma. Even before the girl appeared in front of the House committee, the failure was known throughout the medical community.

Since retroviruses presented difficulties in vivo, attention turned to the adenoviruses—which include the viruses that cause certain types of severe upper-respiratory infections in humans. They worked. "They were wonderful," Verma says. "First of all, you could make billions of virus particles." Secondly, wherever the particles were introduced, the imported genes would be expressed. Many researchers switched to adenoviruses. But they turned out to be highly immunogenic: they are difficult to use safely because they can provoke strong immune reactions. Next came adeno-associated viruses, AAVs. Because they have only two proteins, AAVs provoke the immune system less than adenoviruses do.

The gene-therapy trial that Gelsinger had been participating in was tainted by accusations of overconfidence, haste, negligent administration, and conflict of interest. Yet all this diverted attention from acute and fundamental problems with gene therapy itself.

In the fall of 1994, Harold Varmus, the director of NIH, became increasingly skeptical about the quality of gene-therapy research. The agency's Recombinant DNA Advisory Committee (RAC) was reviewing all protocols for human trials of gene therapy funded by NIH. The committee's first concern was safety. But as its recommendations passed across his desk for final approval, which was normally routine, Varmus realized that the committee was not systematically evaluating the trials' scientific merits.

It turned out that Anderson's were only the most egregious of many extravagant and unsupported claims surrounding gene therapy. Although NIH was giving out $200

million a year for gene-therapy research, and big pharmaceutical firms and swarms of biotechnology startups were thought to be spending as much again, not a single success with humans had been reported in any peer-reviewed journal. In May 1995, Varmus convened a panel headed by Stuart Orkin, a professor at Harvard Medical School, and Arno Motulsky, a geneticist at the University of Washington, Seattle, to review the state of gene-therapy research and assess how funds should be apportioned among gene-therapy research areas.

Orkin and Motulsky reported in December, at length and scathingly. The promise of gene therapy appeared great, but its failures had persisted despite the RAC's approval of more than a hundred protocols. Most clinical trials were too small and exploratory in nature to evaluate the medical merits of the treatment; they lacked adequate controls and rigorously stated goals. Gene therapy, the panelists concluded, had been widely and harmfully oversold.

The balloon was pricked. The RAC had been considering approximately 15 protocols at each of its regular sessions; but the next meeting, scheduled for March 1996, was canceled. No proposals requiring public review had been submitted.

Three years later came Jesse Gelsinger's death.

Gelsinger and the 17 other patients in the trial at the University of Pennsylvania were being treated for a deficiency of the enzyme ornithine transcarbamylase, which the liver uses to break down ammonia, a by-product of protein digestion, into harmless waste products. In its most severe form, the deficiency kills babies in their first year. Gelsinger had been kept alive on a strict diet and a regime of pills. When he learned of the gene-therapy trial, he volunteered.

The trial was carried out at the university's Institute for Human Gene Therapy, which was headed by James Wilson. It was one of the top such centers in the country. The corrective gene was loaded into an adenovirus. The 18 patients were divided into groups that got increasingly large doses. Gelsinger got the biggest—a culture of 38 trillion virus particles. He received the dose on September 13, 1999. By September 15, his vital signs were falling precipitously. With his father's assent, he was taken off life support, and he died on September 17.

Jesse Gelsinger's death was the first directly attributed to gene therapy. An alert went out to the hundred or so experimenters using adenovirus vectors. In the press and in scientific journals, the case was reported as a disaster for the field.

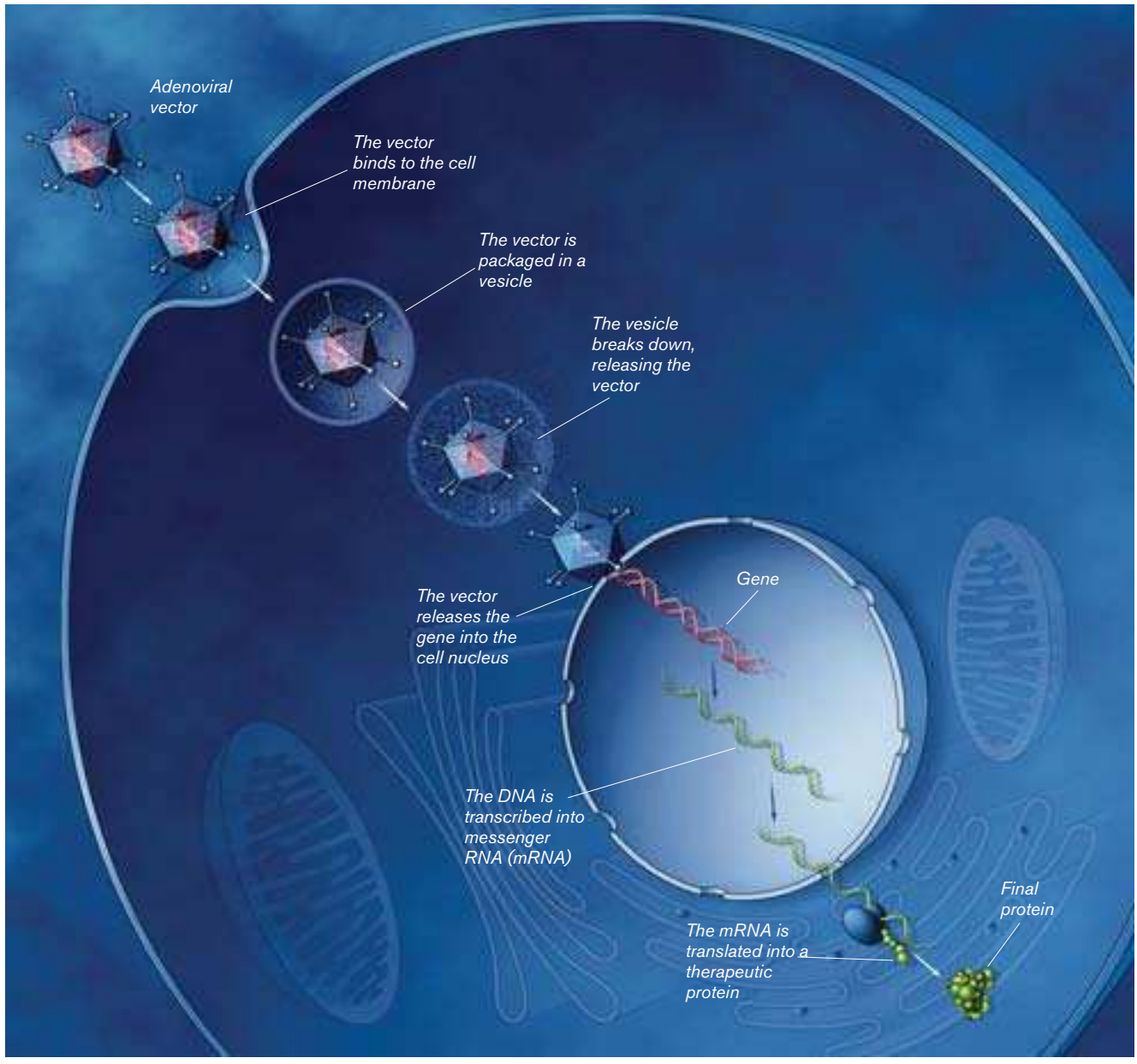
NIH investigated and called a special public meeting for December 8, 9, and 10. The problem became clearer. The protocol for the trials, as approved four years earlier by the RAC and the FDA, had called for the adenovirus vector to be injected intravenously. The FDA had subsequently authorized direct injection of the vector into the hepatic artery, which was the method actually used. Nonetheless, Gelsinger's autopsy found that the vector was widespread in his spleen, lymph nodes, and bone marrow.

Meanwhile, the FDA was conducting its own inquiry. Investigators were harshly condemnatory. Selection of trial participants had been sloppy at best: Wilson and his colleagues were unable to produce proof that any of the volunteers had met the criteria for the trials. Informed-consent procedures had been grossly inadequate. Federal rules require that benefits and risks be explained fully and clearly; Paul Gelsinger, Jesse's father, told the *New York Times* that the family had been led to think the treatment might help Jesse, though the trial had been designed only to test the safety of a treatment being developed for infants. Further, the consent form had failed to mention that monkeys had died after a similar though stronger treatment. In 1992 Wilson had founded a private research company, Genovo, in which he held stock. The company had not put money into this particular study, but it did contribute a healthy portion of the Institute for Human Gene Therapy's overall budget.

On January 21, 2000, the agency ordered a temporary stop to all gene-therapy trials at Wilson's institute. In 2005, Wilson settled with the U.S. Department of Justice: he was not to lead any clinical trials regulated by the FDA for five years.

Hope for cures based on gene therapy, it appeared, had all but died with Jesse Gelsinger. But in February 2000, Friedmann gave the opening talk at a Monday-morning session of an annual meeting of the American Association for the Advancement of Science, in Washington, DC. He reviewed the fundamental difficulties of gene therapy, spoke of the many hundreds of protocols approved but so far not productive. He reminded his audience of Varmus's impatient charge in 1995 that the field had been wildly oversold. Then—with a marked change in tone—he said, "We are on the verge of therapeutic efficacy."

Two lines of work seemed to him to "have the feel of being correct." A pair of American laboratories were beginning clinical trials of gene therapy for hemophilia. Proper blood clotting requires a cascade of responses, controlled by a series of proteins. Hemophilia A, the most common form of the disease, is caused by a defect in the gene for one of those proteins, factor 8; hemophilia B is caused by a defect in the gene for another, factor 9. The study Friedmann thought had that "sense of correctness" came from work with hemophilia B by Katherine High, a hematologist at the Children's Hospital of Philadelphia. At Stanford, the gene therapist and virologist Mark Kay was also working with hemophilia B. Kay and High had combined their efforts.



Their methods worked with animal models of the disease. They were ready to start human trials.

But the most convincing results, Friedmann said, were just then coming from a group of pediatricians in Paris. Their leader was a man named Alain Fischer, a clinician working with small boys who had a form of SCID. Like the girls whom NIH's Anderson had treated for ADA deficiency, these children produced no T lymphocytes, the white blood cells that fight infection. But their disorder was caused by a different gene. The children had been sick; they were not thriving. Then Fischer and his colleagues tried gene therapy. "These kids are now to all appearances immunologically reconstituted entirely," Friedmann said. "All their immune properties seem to be

Inserting a Gene

Genetically engineered viruses are often used as "vectors" to carry desired genes into cells. Here, an adenovirus has had a therapeutic gene inserted into it. Gene therapy takes advantage of viruses' natural ability to use the cellular machinery to express the viral genes. The final result, however, is a desirable therapeutic protein rather than more viruses. Many different types of viral vectors have been used in gene-therapy experiments, including retroviruses, adeno-associated viruses, and, most recently, lentiviruses—a type of retrovirus that includes HIV—stripped of their pathogenic genes. None of these viral vectors, however, has been without problems.

optimized." He went on, "And the thing that's so impressive about it is, first of all, that it came from nowhere. It came from left field." Experts on immune-system disorders "certainly must have known of Alain Fischer and his group," Friedmann said, but the gene-therapy community was not as familiar with his work. "And it also is presented in meetings in a very low-key, very modest sort of way," Friedmann said. "They say straight out there's nothing new in method—they've done just a combination of a fortuitously good disease model [with] a lot of standard retrovirology that's been developed over many years."

Fischer and a dozen colleagues reported their method, and their success with their first two patients, in *Science* on April 28, 2000. They followed up with a report in the *New England Journal of Medicine* for April 18, 2002.

Meanwhile, Mark Kay and Katherine High reported that when they injected their vector into dogs with hemophilia B, the dogs had a therapeutic response. Avigen, a biotech company headquartered in Alameda, CA, collaborated with High and Kay to plan clinical tests of the treatment's safety in people.

In November 2002, the French scientists halted their trials. The number of patients was up to 10, but now one of those patients who'd gained a fully normal immune system had come down with a disease similar to leukemia, out-of-control proliferation of the very white blood cells that had been restored.

Then the June 4, 2004, issue of *Science* reported that Avigen had backed out of the trials of the hemophilia treatment. Two of seven patients had developed slightly elevated levels of liver enzymes.

On September 28, 2005, I went to see Alain Fischer at the Hôpital Necker, a children's hospital in Paris. He was direct and clear. "I'm not a specialist in gene therapy," he said at once. "My real field is immunology and, within immunology, genetic diseases of the immune system." He had been working with these diseases for 25 years. "I am a physician. And here there is a clinical unit where children with immunological diseases are taken care of. So that's where I'm starting from." What kinds of diseases? "All kinds," he said. "From deficiencies in T lymphocytes, B lymphocytes, innate immunity, there are … " He drew breath. "We don't know yet exactly. There are at least 140 different immunological diseases." He added, "They are all very different."

Fischer went on, "We are not going to become specialists in gene therapy—that is, to try to adapt gene therapy to different diseases. This is not our goal. We are specialists in these immunological diseases, and gene therapy is one strategy to try to treat these patients." He was drawn to gene therapy in the early 1990s, when a new gene was identified that, mutated, causes a form of SCID. He had encountered patients with the mutation. "We understood very quickly, within one to two years, the pathophysiology of the disease," Fischer recalled. "And we realized at that time that this disease could be the best candidate to test gene therapy." The need for some type of effective treatment was certainly dire. Like all forms of SCID, he said, without treatment this one kills within the first year of life. The only treatment was bone-marrow transplants; but their success rate plummets unless close to identical immune-system matches can be found, and that's possible only about 20 percent of the time.

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The types of cells affected by the disease also made it a good candidate for treatment with gene therapy, Fischer said. First, when the gene in which the mutation occurs is functioning properly, it encodes a protein that is vital if the precursors of T lymphocytes are to survive and proliferate. Second, unlike other types of immune system cells, T lymphocytes can survive for decades—sometimes even for an entire lifetime.

These two facts meant that even if the researchers could genetically alter only a few precursor cells, these cells might develop—or, as the scientists say, "differentiate"—into a large number of mature T cells that had a lasting benefit for the patient. "So we had the hope," Fischer said, "that a very poor technology could—in that context, with that disease—work."

Then came the drudgery. "We made vectors, retroviral vectors, the best technology of the time, blah blah blah," remembered Fischer. But the tests went well. By 1998, Fischer and his colleagues were ready to seek approval to start human trials.

The first trial began on March 13, 1999. "And between '99 and 2002, we had treated 10 patients," Fischer said. The researchers took bone marrow containing the lymphocyte-precursor cells from the patients. In cell culture, they introduced the vector, a disabled retrovirus with the correcting gene. After several days, they injected the cells back into the patients. "And in nine out of ten, we were pleased to see that it worked," he said.

As Fischer and his team had expected, the number of treated precursor cells able to generate T cells was very low. However, he said, it was sufficient to produce a normal number of T cells. "After a few months, these children could leave the hospital and start to live normally with their parents. And except for those who had the complication I'm going to describe in a moment, they are living normally still today."

After the first three years, three of the ten children treated developed a severe complication, an uncontrolled proliferation of T lymphocytes. "I would call it a leukemia-*like* disease," said Fischer. Childhood leukemia can usually be cured with massive doses of chemotherapy, and that's how Fischer and his colleagues treated the three patients. One died. "The other two kids today are doing well, as well as the other seven," Fischer said.

How much did all this cost? "A lot!" Fischer laughed abruptly. "A lot; but the treatment of a child with such a disease, without gene therapy, costs a lot, too." Yes, he said, per patient, the cost of the research is huge. But "the cost of the therapy itself is not that big. Let's assume it's commercialized. I would assume the cost of the therapy itself, with the cost of the vector—the cell treatment ex vivo—shouldn't cost more than maybe somewhere between $30,000 and $50,000, something like that. Per patient." About the same as a heart transplant? "Exactly!" he said. "As it moves toward being a kind of, quote, 'routine therapy,' this is not much higher than many other therapies."

And those complications? "We'll see when we have enough follow-up to be sure," he said, adding that if the chances of such a complication were reduced by a factor of 10, he'd consider the risk-benefit ratio "perfectly acceptable." Fischer said he does not yet know whether his methods can be generalized to other types of genetic defects; he is not making any sweeping claims. His group is moving first to two other immune-deficiency diseases, involving other genes. "So we want to go step by step from the ones that are easiest to the most complex."

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From the first glimmer of possibility to the present day, Theodore Friedmann has written and spoken as gene therapy's most ardent advocate. He has seen medicine enter a new era, which offers "new and definitive approaches to therapy that were previously only the stuff of dreams and scientific fantasy." His has also been a voice of caution, of reason. He has had to warn his colleagues that they must openly address their discipline's difficulties, its limitations, its failures. Yet he continues to marvel at the unprecedented possibilities raised by gene transfer. For the first time, he says, and one can sense his quiet exultation, medicine can do more than treat the signs and symptoms. It can reach the underlying causes. It can cure. "It's going to be difficult," he says. "Yet medicine has always had to work with imperfect knowledge and technology." TR

Horace Freeland Judson is the author of five books, including The Eighth Day of Creation, *a history of molecular biology that was published in 1979 and is still in print.*

By James Surowiecki

Philanthropy's New Prototype

Can Nicholas Negroponte get governments to buy cheap laptops?

In the decades after the Civil War, libraries were scarce in much of the United States. Many towns had no library at all, and those libraries that did exist were typically small and private, run by clubs or lodges that had scraped together collections of books to lend to their members or, on occasion, to outsiders who paid a fee for borrowing privileges. For the most part, towns did not have library buildings; book collections were housed instead in cheap offices or in unused space in public buildings. Even in bigger cities, it was often difficult to borrow books. Until the very end of the 19th century, Pittsburgh, for instance, had just one private lending library, and it struggled to stay afloat. And few people, if any, took seriously the idea that every town in the country should have a public library where citizens would have free and equal access to books.

Andrew Carnegie changed all that. Carnegie was an embodiment of the American Dream; born poor in Scotland, he had emigrated to the United States and built a fortune in the steel industry, turning himself into one of the country's wealthiest and most powerful businessmen. As Carnegie told it, when he was a young boy, he'd had to work instead of going to school. But a wealthy local man named Colonel Anderson had put together a small library of about 400 books, and every Saturday, Carnegie was allowed to read and borrow some of them. The experience, Carnegie wrote later, convinced him that there was no more productive way to help children develop than to build public libraries. And so, beginning in the 1880s, he set out to do just that, in towns all across the country.

Strictly speaking, Carnegie began his campaign outside the United States; his first library, built in 1881, was in his hometown of Dunfermline, Scotland. The first library he built in the United States, eight years later, opened in Braddock, PA, where Carnegie Steel had one of its biggest mills. A year later came the Carnegie Free Library of Allegheny, PA. The Allegheny library was important because it was the first funded according to the model that Carnegie would follow thereafter: instead of simply paying for and endowing the library, he offered the town a large initial grant on the condition that it agree to pay for the library's operations thereafter. (In what came to be known as the "Carnegie formula," towns generally committed to an annual budget—for maintenance, new books, and so on—that equaled 10 percent of Carnegie's original gift.) These were, in other words, to be genuinely public libraries, dependent not on the largesse of a single person but on communities' willingness to subsidize their own access to knowledge.

That willingness was not always easy to inspire; in some towns it was actually illegal at first to use tax money to pay for libraries. But as more towns accepted Carnegie's deal, and as it became evident that the libraries were generally very popular once they were built, more towns decided that they, too, needed free libraries. By the time he died in 1919, some 30 years after the Allegheny library opened, Carnegie had given away $350 million of his fortune; he spent more than $60 million of it to build more than 2,800 libraries, including almost 2,000 in the United States and almost 700 in Great Britain. His donations had so effec-

TARA HARDY, COLAGENE.COM


Education is freedom

One Laptop per Child does not yet have a working machine to sell to interested countries, but it expects to have what it calls "B machines" ready for testing by mid-November (this issue went to press in late October). Pictured above are various prototypes; the one at the far right is closest to the final version. OLPC is pursuing options for a human-powered energy source, such as a foot pedal or a pull string, but has dropped the idea of a hand crank.

COURTESY OF FUSE:PROJECT

tively revolutionized public opinion that by the middle of the 20th century, it was the rare American town that dared go without a public library.

Carnegie is usually talked about today as a precursor to people like Bill Gates and Warren Buffett, multibillionaires who have dedicated most of their wealth to philanthropic endeavors. But when you look at the way Carnegie built libraries—seeding institutions around the country and encouraging local involvement in the hope of convincing people of the virtues of free access to knowledge—what it calls to mind most is not Gates's prodigious effort to fund the fight against infectious diseases but, rather, an endeavor called One Laptop per Child (OLPC)—or, as it's colloquially known, the $100 laptop.

The $100 laptop sprang from the fertile, utopian mind of tech guru Nicholas Negroponte, who is the cofounder and chairman emeritus of the MIT Media Lab, a successful venture capitalist, and the author of *Being Digital*, the 1995 paean to the digital economy. The concept behind the project, which Negroponte unveiled at the World Economic Forum in Davos, Switzerland, less than two years ago, is as simple as its name: give all children in the developing world laptop computers of their own. If we achieved that, he believes, we could bridge what's usually termed the "digital divide." The laptops would offer children everywhere the opportunity to benefit from the Internet and would enable them to work with and learn from each other in new ways. OLPC, the nonprofit organization that Negroponte set up to manage the project, has taken responsibility for designing the computer and engaging an outside manufacturer to produce it. But the nonprofit is not going to buy the computers. That, at least for now, is the responsibility of governments, and Negroponte has said that the $100 laptop will not go into production until he has firm commitments from governments to buy at least five million units. Would (or should) any government be willing to lay out the cash? Negroponte answers that question with characteristic bluntness. "Look at the math: even the poorest country spends about $200 per year per child. We've estimated what a connected, unlimited-Internet-access $100 laptop will cost to own and run: $30 per year. That has got to be the very best investment you can make. Period."

Despite the appeal of this vision, Negroponte's project has attracted skepticism as well as support. In part, that's because of Negroponte himself, whose self-assured optimism makes him a permanent lightning rod. More than that, though, OLPC is effectively trying to do two dramatic things at the same time. It's trying to lower the cost of computing to the point where it's accessible to the world's poor—which is to say, to most of the world's population. And it's trying to succeed with a new model of philanthropy, albeit one that harks back to Carnegie—blending private, nonprofit, and governmental interests to create a project of vast scale and scope on a budget that is, even by philanthropic standards, surprisingly small.

Of course, this will only work if OLPC can deliver on its promise, and the problem is that at this moment you cannot buy anything resembling a computer, much less a portable one, for a hundred dollars. OLPC had to design and

COURTESY OF DESIGN CONTINUUM (CRANK); COURTESY OF FUSE-PROJECT

build an entirely new kind of laptop from scratch—one that would endure rough handling, function even in the absence of a steady power supply, and allow easy networking and Internet access, and whose readable if small screen would use startlingly inexpensive technology. Not surprisingly, critics doubted that it was possible. Yet in the past year, Negroponte has lined up an impressive array of partners to furnish the innards of the computer, including AMD and Red Hat, while Quanta, the Taiwanese manufacturer that currently makes around a third of the world's laptops, is on board to manufacture the machines.

OLPC designers claim to have cracked the toughest problems they faced. When the laptop is not plugged in, it can be powered by means of a foot pedal (or pull string, depending on the final decision) that will generate 10 minutes of power for every minute of exertion. Out of the box, the laptops will connect with one another to form a mesh network that will make each computer a transmission node, allowing the laptops to talk to each other and greatly magnifying the range of any Internet connection. And the screen will have both a high-resolution black-and-white mode, in which it will be readable even in bright sun, and a backlit, lower-resolution color mode. The designers say the display will be at least as readable as today's LCD screens but use far less power, and they expect it to cost about $35, which is roughly a quarter of what a typical screen costs today. It will be a very small screen for a laptop—seven and a half inches—but if it works, it will represent a genuine engineering breakthrough.

Nevertheless, the $100 laptop is not yet a reality. (In fact, the name is something of a misnomer: for more than a year now, Negroponte has been predicting an initial cost of closer to $150, though he expects that, as with most electronic products, the laptop's price will fall as time goes on and units are produced in greater volume.) OLPC has yet to demonstrate a working version of the laptop; Negroponte says that the first working models, so-called B machines, will come off the assembly line in November, after which they'll be put through a torture course of testing in five developing countries—Brazil, Argentina, Libya, Thailand, and Nigeria—to see how they hold up. And even if they do work, the task of persuading governments to buy them still remains. Negroponte has made real progress on this front. In October, Libya signed a memorandum of understanding that effectively commits it to buying a million laptops, assuming the B machines pass their tests, and the other four test nations seem nearly as likely to sign up if the machines work as planned. But five million laptops is, by OLPC's self-defined standards, just a start. No matter how well things go in the next few months, Negroponte can almost certainly count on continuing to spend a great deal of time negotiating with government ministers around the globe. In that sense, just as we're waiting to see whether OLPC's laptop will work, we're waiting to see whether its "business" model will work, too. If it doesn't, the project will be remembered as an interesting side note in the history of computing. If it does, OLPC will become integral to one of the more remarkable narratives of the past decade: the revolution in philanthropy.

Enterprising Philanthropy

As the names of the Carnegie, Ford, and Rockefeller Foundations suggest, American philanthropy has always depended heavily on American businessmen. But with some exceptions—like the Carnegie libraries, or the Salvation Army, which Peter Drucker once called "the most

effective organization in the United States"—the fact that foundations were mostly funded by business did not mean they were businesslike in their approach. Over the last decade or so, that has changed dramatically. Beginning sometime in the mid-1990s, two trends came together to remake philanthropy in the United States: the tremendous boom in the U.S. economy and stock market, and a growing desire on the part of wealthy businesspeople to apply their moneymaking techniques to other, less commercial endeavors. The economic boom meant a lot more money floating around: charitable donations in the United States rose 10 percent annually in the late 1990s. It also meant a lot of newly wealthy people, many of them entrepreneurs, who were interested in figuring out how to spend that money in the smartest way possible. The result has been an explosion in new forms of philanthropic investment and a concentrated effort to identify what might be thought of as the philanthropic equivalent of business opportunities: areas where neither business nor government has been meeting a need. And although the growth in charitable donations slowed with the stock-market crash and recession, it's picked up again, with donations rising about 23 percent between 2001 and 2005.

Some philanthropies are taking on immense global problems. The Gates Foundation, most obviously, has become one of the world's most forceful promoters of research on malaria, tuberculosis, and AIDS, while Bill Clinton is currently raising billions to improve AIDS treatment and research. Some are taking on smaller, local problems. The Acumen Fund, for instance, operates as a kind of philanthropic venture capital fund, working with companies in the developing world on products and services designed specifically to serve the four billion people who live on less than $4 a day; its projects include drip-irrigation kits in India and malaria nets in Africa. The Omidyar Network funds both profit-seeking and nonprofit enterprises, while Google's various philanthropic enterprises invest in everything from traditional nonprofits to projects like OLPC to for-profit ventures.

What all these organizations have in common is a much greater focus on the return they get on their investments in charities, with "return" defined more in terms of its social than its financial value. Often, they explicitly demand that grant recipients meet performance goals just as any corporate division would be expected to. The premise is that it's possible to bring greater rationality not only to the grantmaking process but to the actual operations of philanthropic organizations. This new model is sometimes called "high-engagement philanthropy": just as venture capitalists often play an important role in shaping the strategies of the companies they fund, these new foundations tend to be more directly involved in their grantees' operational decisions.

One Laptop per Child is part of this broader movement: though it is receiving grants rather than making them—Google and News Corp. are among its donors—it is an excellent example of the application of business logic to social problems. From one angle, in fact, OLPC looks more like a company than like a traditional charity, in the sense that it is designing and marketing a product and outsourcing its production to firms that are expecting to make a profit. Instead of circumventing the market, then, OLPC is working within it, and Negroponte is counting on the efficiencies generated by market processes to drive the price of the laptop down over time. At the same time, because OLPC is relying on governments to buy its product, it needs to spend a great deal of time lobbying and cajoling government officials, a task that is very familiar to activist organizations.

OLPC is unusual in relying on three different kinds of enterprises—private, nonprofit, and governmental—to carry out its mission. On the one hand, this structure arguably makes the project more robust, since OLPC can draw on the different strengths of each. On the other hand, it also makes things more complicated. Negroponte, for instance, says all his advisors believed that OLPC would need to be a for-profit company in order to attract the necessary talent. ("They were wrong," he says.) More important, because OLPC is not simply a charity, it has a much harder time making things happen than it would if it were giving money away. Dealing with governments is not easy, particularly since OLPC has initially chosen to try to do business primarily with big governments: Argentina, Brazil, Nigeria,

From one angle, OLPC looks more like a company than like a traditional charity: it is designing and marketing a product and outsourcing its production to firms that are expecting to make a profit. Instead of circumventing the market, then, OLPC is working within it, and Negroponte is counting on the efficiencies generated by market processes to drive the price of the laptop down over time.

Thailand, and China. (Perhaps it's not a coincidence that it was a small country, Libya, that was the first to make a commitment to the project.) "Governments are hard; large governments are harder; ministries of education are harder," Negroponte says. "So we have indeed tackled the hardest of the hardest of the hard." The course of OLPC's efforts in this sphere has not run entirely smooth. In June, Sudeep Banerjee, India's education secretary, wrote a letter to fellow members of his government saying that the country was not interested in buying laptops for its students and that "we cannot visualize a situation for decades" that would justify the program. China, however, remains a possibility. Negroponte has met with the Chinese minister of education twice.

For all the challenges that OLPC's odd structure presents, though, it's hard to see how such a novel project could succeed, at the scale Negroponte has in mind, as either a charity or a for-profit company. "We'd like to move five to seven million units in our first year," says Ethan Beard, a Google employee who sits on the board of OLPC. "That's already a pretty sizable amount of money. But eventually, we'd like to move 20 million units a year, which is $2 billion or more, and there are very few, if any, nonprofit institutions that could handle a project of that size." And had OLPC been a for-profit company, persuading governments to buy the $100 laptop would have been far more difficult. "If you're going to be going in to government ministers and pitching them on education, especially with a project this new and ambitious," Beard says, "you need to be able to say, 'We're not doing this to make money,' because otherwise your motives are always going to be in question." Interestingly, there may be at least one important exception to this rule. "China does not understand nonprofit structures," Negroponte says, "and many people just cannot believe we are doing this philanthropically."

The Critics

From the start, there have been objections to the $100 laptop. Many people simply assumed that the project was hopeless, that there was no way to build a functioning laptop at that price and no way to enlist partners with adequate resources. "Let's see, build Xbox 3 for Microsoft or build PCs for charity. Hmm, tough choice there," wrote Doug Mohney of the technology website the Inquirer; Tony Roberts, the CEO of the U.K. charity Computer Aid International, said the entire project was based on a "misunderstanding of the history of technology." Others insisted, and continue to insist, that even if a real machine is produced at the end of all this, it will be little more than a toy. In December 2005, Craig Barrett, the former CEO of Intel, dismissed the product as a "$100 gadget."

More substantively, and more recently, critics have charged that as a means of bridging the digital divide, the $100 laptop is simply the wrong technology. The success of the laptop, the argument goes, depends on building an entirely new infrastructure in the developing world, rather than relying on the infrastructure that's already there. In OLPC's early stages, there appeared to be a good chance that Microsoft would supply the laptop's operating system. But around the time that deal fell through—Negroponte decided to keep the software open source—Bill Gates and Craig Mundie, Microsoft's chief research and strategy officer, were proffering an alternative to Negroponte's plan, in the form of an amped-up cellular phone for the developing world. Cell phones—and cell towers—are ubiquitous in the Third World, and they're already somewhat affordable, whereas Internet connectivity is much harder to come by. Most of what can be done on an Internet-connected laptop can also be done on a cell phone, albeit more slowly and less comfortably. Gates and Mundie argue, essentially, that we would be better off using this existing infrastructure to put Net-enabled cellular phones in the hands of kids and parents than trying to build something from scratch. In July, Mundie unveiled a rough prototype of Microsoft's phone, called FonePlus, and suggested that it would eventually allow users to read e-mail, run applications like PocketOffice, and surf the Web. It's also possible that the phone could be hooked up to a TV and a keyboard.

The simplest and strongest argument against the $100 laptop, though, is that even if it can be built, and even if it will work approximately as well as Negroponte promises it will, it's still a waste of money. In an ideal world with unlimited government budgets, the argument goes, putting a laptop in the hands of every child would be a marvelous and valuable feat. But in the far-from-ideal worlds of developing countries, which generally have limited budgets and pervasive social problems, millions or billions of dollars' worth of computers are a luxury that governments can ill afford. Brazil, for instance, which seems likely to buy a million laptops from OLPC as soon as they become available, has around 45 million school-age children: equipping all of them would cost something like $6.3 billion. Given the desperate poverty of many Brazilians, are laptops the best use for that kind of money?

The technology website ZDNet U.K. put it this way: "If Bill Gates and $100 laptop progenitor Nick Negroponte were to look at the places without light and listen to those without a voice, a laptop per child would not be first on the list." Philanthropists' efforts would be better directed, in other words, to figuring out ways to help the truly needy. The reality is that in most countries, towns don't even have libraries. Are we really better off spending money on computers instead? When the Indian education secretary wrote his letter in June declaring that India

would not be participating in the program, he made precisely this point, arguing that there were more cost-effective ways to improve student performance than buying laptops from OLPC. This objection carries so much weight precisely because of OLPC's unusual structure. If the organization were purely a charity, building and buying the computers with its own money, we might question its priorities, but we all know that charities spend billions of dollars every year on less-than-urgent projects with which their donors are obsessed. And we accept this, because we assume it's better that money get spent on some philanthropic endeavor than on none. In the case of OLPC, though, tax dollars are at stake.

Ultimately, the critiques of OLPC can be divided into two types: those having with to do with technology and those having to do with what one might describe as ethics. Some of the technological objections can seem frivolous: a machine with a readable 7.5-inch screen, three USB 2.0 ports, power-saving features, 512 megabytes of flash memory, and a working operating system is not a "gadget." Some will be answerable only a few months from now, when we find out whether the laptop passes its field tests. As for the argument that cellular phones will be a better route to Internet access in most of the developing world for the foreseeable future, their advantages have to be balanced against their disadvantages: a minuscule screen and no keyboard. "Suggesting that cell phones are an alternative is like saying we can use postage stamps to read textbooks," Negroponte says. "Books have a purposeful size, based on how the eye works and the ability to engage peripheral and foveal vision at the same time for browsing. It is not by chance that atlases are bigger than timetables." It is true that connecting the phone to a keyboard and a television would yield what amounts to a personal computer. But that would erode the cost advantage of cell phones and, worse, tether students to particular spots (assuming, of course, that they even have televisions).

And while connecting laptops to the Internet is obviously fundamental to OLPC's vision of how the project will change kids' lives, the mesh-networking technology embedded in the laptops will be valuable even when Internet connections aren't available. "To me, nowadays, a computer that's not connected to the Net is useless," Beard says. "But allowing kids in a school to network all of their computers together, even when they're not on the Net, is actually important from an educational point of view, because it allows them to collaborate and to learn from each other in a way that they wouldn't have been able to before." In any case, cell phones don't need to lose if OLPC wins, and vice versa: on the contrary, it's clearly best for the developing world if lots of companies and nonprofits are competing to supply them with new technologies.

PLUGGED IN **Nicholas Negroponte and United Nations secretary-general Kofi Annan promote One Laptop per Child at the World Summit on the Information Society in November 2005. Annan called the initiative "a truly moving expression of global solidarity."**

ERIC FEFERBERG/AFP/GETTY IMAGES

It may be difficult for poorer governments to justify spending a good chunk of their education budgets on laptops. But the reality of both philanthropic and government spending is that money often goes to projects that do not help as many people, or people who are as needy, as other projects might. These projects may not be perfect, but they can still do tremendous good. In the post-Reconstruction United States, after all, there were lots of worthwhile things Carnegie could have done with his money; in fact, in many of the towns where he built libraries, citizens grumbled that their tax dollars should be going to something that really mattered. Yet in the long run, one would be hard pressed to say that either Carnegie or the taxpayers wasted that money, because the social benefits of disseminating knowledge are so immense.

Similarly, it may be a mistake to assume that technology is something only wealthy nations can afford, and that poorer nations are better off concentrating on basics like health and water. On the contrary, a country can, as the

PITCHING THE WORLD **In June 2005, Negroponte met with Brazilian president Luiz Inácio Lula da Silva at the Planalto Presidential Palace. Brazil is now poised to buy one million laptops from One Laptop per Child. Argentina, Nigeria, and Thailand are also good prospects, and Libya has made the firmest commitment yet.**

prime minister of Ethiopia recently put it, be "too poor not to invest in information and communications technology." Information technology is often a useful way of improving connections to the outside world, and thus creating greater possibilities of exchange. And for children, access to new technology promises to speed learning dramatically. "I have not met anybody who claims they are too poor to invest in education, nor anybody that said it was a waste of money," Negroponte says. "If somebody is dying of hunger, food comes first. If somebody is dying from war, peace comes first. But if the world is going to be a better place, the tools for doing so always include education."

It may seem curious to buy laptops where there are no libraries, but the promise is that computers will bring the world's libraries inside a student's home. Despite the element of wishfulness in this vision, the idea that the Net allows countries to leapfrog traditional stages of development is almost certainly correct. C. K. Prahalad, the University of Michigan professor whose book *The Fortune at the Bottom of the Pyramid* analyzes the tremendous market opportunities in the developing world, argues forcefully that these countries are surprisingly fertile ground for new technologies. "We assume that the poor will not accept technology," he says. "The truth is, they will accept technology in some ways even more easily than we will, because they have not been socialized to anything else. They accept technology rapidly, as long as that technology is useful. We have a very long forgetting curve. They don't. They have only a learning curve."

It is, in any case, important to recognize that the $100 laptop is not currently being pitched to truly poor countries, although Negroponte certainly envisions them as eventual customers. On the contrary, the five nations currently on track to buy the laptops—Libya, Brazil, Argentina, Nigeria, and (even after the coup that removed Prime Minister Thaksin) Thailand—all have relatively healthy economies and relatively large state budgets. That makes it considerably easier for them to justify investing in a new technology, particularly one that seems to offer the prospect of mitigating one of the biggest problems they face: the sharp divide between rich and poor. It also means that the $100 laptop could have a bigger impact sooner than it might otherwise, since the students likely to receive it first would use it to expand on skills they already possess; students in very poor countries, by contrast, are more likely to be illiterate and innumerate.

While those involved with OLPC seem genuinely confident that the project will work, it could still be derailed by any number of problems. The laptops could end up being stolen from kids and resold, or the distribution of laptops could simply create a new digital divide. (In Brazil, after all, one million kids will suddenly have laptops, and 44 million won't.) More important, relying on governments to buy a product guarantees that the process will be capricious (especially in the case of undemocratic regimes), and certainly Negroponte's failure to get India to commit to the project was a blow to at least its short-term prospects. But even if we don't know whether OLPC will succeed, we do know that if it does, it will represent a dramatic step forward for both computing and philanthropy.

What OLPC will have done, after all, is figure out how to put computing power in the hands of millions more people by using dramatically new technologies. Just as important, OLPC will, should it succeed, serve as a new model for getting the nonprofit, private, and public sectors to work together efficiently and productively. In part because of frustration with government corruption and bureaucracy, and in part because of the American preference for private rather than public solutions to social problems, the idea of working with governments in the developing world has become increasingly less attractive to philanthropists. But there are problems too big to be solved by NGOs or corporations (or governments, for that matter)—problems that demand new kinds of alliances. OLPC is, in that sense, not just building a new computing machine. It's also building a new philanthropic machine, one as cobbled together and untraditional as the $100 laptop. The question that remains is just how well either of those machines will really work. TR

James Surowiecki is the financial columnist at the New Yorker *and the author of* The Wisdom of Crowds.

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Silicon and Sun

In his lab facing the Pacific Ocean, Daniel Morse is learning new ways to build complex semiconductor devices for cheaper, more efficient solar cells. He has an unlikely teacher: sea sponges. **By Kevin Bullis**

In his beachfront office overlooking the Santa Barbara channel, Daniel Morse carefully unwraps one of his prized specimens. An intricate latticework of gleaming glass fibers, it looks like a piece of abstract art or a detailed architectural model of a skyscraper. But it's actually the skeleton of one of the most primitive multicellular organisms still in existence—a species of marine sponge commonly known as Venus's flower basket. Morse, a molecular biologist at the University of California, Santa Barbara, wants to know how such a simple creature can assemble such a complicated structure. And then he wants to put that knowledge to work, making exotic structures of his own.

The lowly sponge has come up with a remarkable solution to a problem that has puzzled the world's top chemists and materials scientists for decades: how to get simple inorganic materials, such as silicon, to assemble themselves into complex nano- and microstructures. Currently, making a microscale device—say, a transistor for a microchip—means physically carving it out of a slab of silicon; it is an expensive and demanding process. But nature has much simpler ways to make equally complex microstructures using nothing but chemistry—mixing together compounds in just the right combination. The sponge's method is particularly elegant. Sitting on the seabed thousands of meters below the surface of the western Pacific, the sponge extracts silicic acid from the surrounding seawater. It converts the acid into silicon dioxide—silica—which, in a remarkable feat of biological engineering, it then assembles into a precise, three-dimensional structure that is reproduced in exact detail by every member of its species.

What makes the sponges' accomplishment so impressive, says Morse, is that it doesn't require the toxic chemicals and high temperatures necessary for human manufacture of complex inorganic structures. The sponge, he says, can assemble intricate structures far more efficiently than engineers working with the same semiconductor materials.

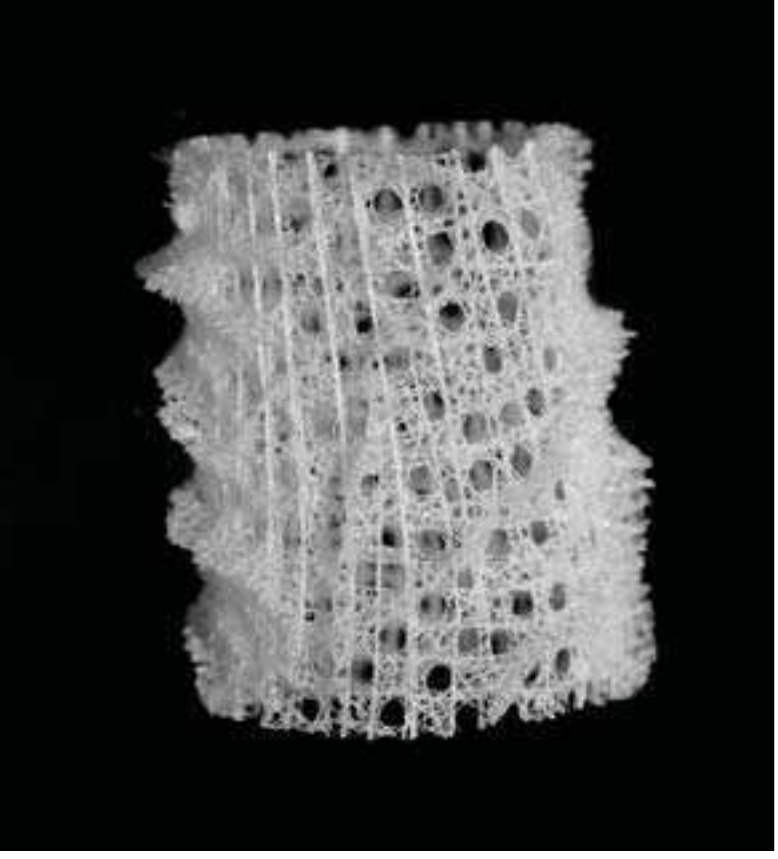
This primitive creature and a number of other marine organisms have become an inspiration for researchers who hope to find simpler and cheaper ways to build inorganic structures, such as semiconductor devices, for use in computer microchips, advanced materials, and solar cells. The goal is to make silicon and other inorganics self-assemble into working electronics in the same way that the sponge assembles silica into complex shapes *(see "Others in Bio-Inspired Materials," p. 61)*. Energy-intensive, billion-dollar semiconductor fabrication facilities might then be replaced by vats of reacting compounds. But while practical industrial processes are still some way off, scientists are coming to understand how sponges and other sea creatures perform their microengineering miracles.

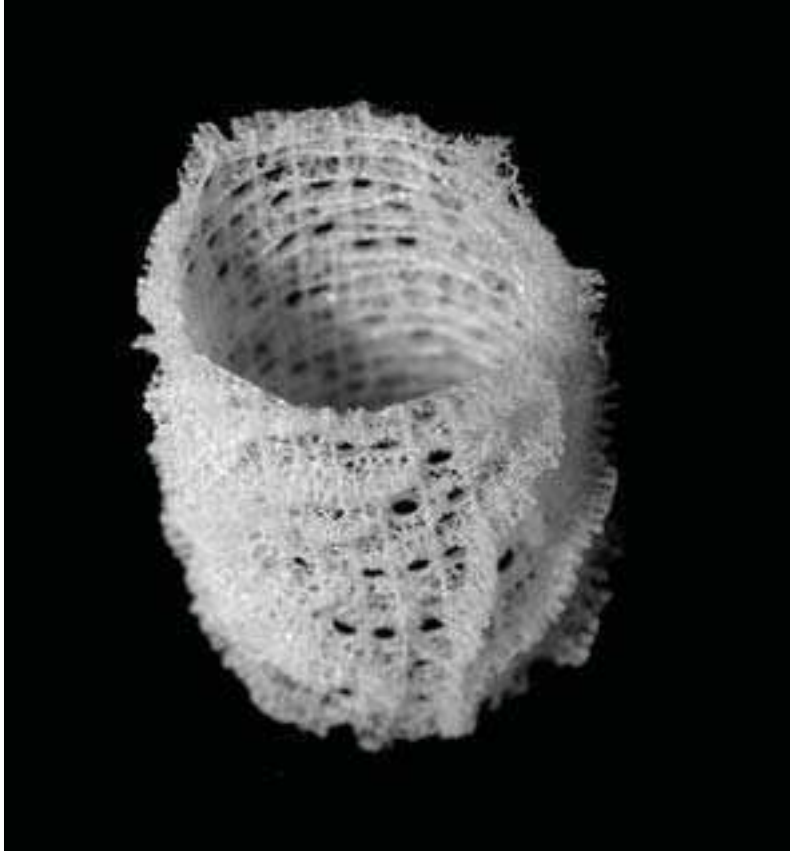
Morse and his team, for instance, are already using biological tricks learned from the sponge to make new forms of semiconductors with intriguing electronic properties, including the ability to convert light into electricity—properties that could be useful in making cheaper, more efficient solar cells. His group, says Morse, is building "structures that had never been achieved before."

Start from Scratch

The seawater tanks outside Morse's lab are teeming with colorful starfish and corallimorpharians, exotic creatures similar to sea anemones. But Morse and James Weaver, a postdoc in the lab, are more interested in an unremarkable-looking rust-colored blob: an orange puffball sponge, a type of sponge that ordinarily lives in rock crevices just off the Santa Barbara coast. If the Venus's flower basket is the glass cathedral of sponges, this is the straw hut. The shapeless creature appears not to have a skeleton at all; but once the

GREGG SEGAL





GLASS HOUSE **This section of a Venus's flower basket sponge, with a layer of living cells dissolved away, shows off its skeleton of cross-braced glass fibers.**

researchers dissolve away the living material of its exterior, a handful of tiny glass needles remain, each only two millimeters long and thinner than a human hair.

Although Morse ultimately wants to understand sponge skeletons that are more complex, these simple needles are a good place to start. Scientists have long known that at the core of the glass needles are strands of proteins, but no one understood what they did or how they related to the needles' construction. So Morse and his colleagues began by isolating the genetic code for one of the proteins—which as a family they came to call "silicateins"—and ran their results through a huge database of known proteins. They weren't expecting a match, but they found one—immediately. The protein was similar to a protease, an enzyme found in the human intestine that is involved in the breakdown and digestion of food.

"It was very bizarre," says Weaver. "Why does the protein that templates the formation of the glassy skeleton of a sponge have anything to do with a protease?" The researchers began to suspect that the silicateins did more than merely serve as a passive template. Indeed, they found that unlike any other enzyme previously studied, a silicatein can do double duty. It actively produces building materials such as silicon oxide—in a sense, by digesting compounds in the seawater—and then causes the materials to line up along its length to form the needle-shaped glass of the sponge skeleton. No such enzyme had been discovered, Morse says, "in all the study of biomineralization, which has gone on for a couple of hundred years."

Morse reasoned that if silicateins were so good at producing silicon oxide, they might also be able to produce the types of metal oxides that make good semiconductors in electronics and in some kinds of solar cells. He was right. "At 16 degrees Celsius, the temperature at which the sponge lives in the cool water right offshore from our lab," Morse says, "this enzyme will catalyze the formation and stabilize the formation of crystal forms of metal-oxide semiconductors that can't be made conventionally except at very high temperatures."

The result suggested a less expensive way to make semiconductors at lower temperatures, but there was a potential problem: contamination. "A biologist is ecstatic when they get a purity of, say, 90 percent. A chemist is ecstatic when they get a purity of 99 percent," says Morley Stone, a biochemist who directs research in biotechnology and materials for the Air Force Research Labs at Wright-Patterson Air Force Base, near Dayton, OH. "But an electronics engineer or someone else who needs to make devices—they want to see materials that have five nines of purity behind them, at least." He adds, "Oftentimes, when you take these biological approaches, you can grow some interesting things and get some interesting morphologies, but they're nowhere close to having the end-state purity that you would need in a final device."

Morse and his colleagues knew that if they hoped to make semiconductor materials for cheap but efficient solar cells, they would probably need a chemical synthesis technique that took its cue from the sponges but avoided the

KEVIN BULLIS

messy biology. The sponge's secret, they discovered, was that amine and hydroxyl chemical groups in the enzyme produce the silicon oxide and assemble it in the required way. That meant that all the chemicals a new synthesis technique would require could be found in ammonia and water. The researchers found that by mixing molecules containing the metal oxides' precursors into water, and then exposing the mixture to ammonia gas, they could create thin films of highly crystalline semiconductors—materials useful for electronics. "This is the breakthrough that gets us into the domain of practical usefulness," Morse says.

Moreover, the crystals have a complex nanostructure that could improve the performance of photovoltaic devices. Near the surface of the water, the concentration of ammonia gas is relatively strong, so this is where the semiconductor crystal starts to form. As the ammonia slowly diffuses deeper into the water, however, it causes crystals to grow down into the mixture, producing a thin film that is not uniform but rather comprises a network of needles or flat plates each merely a few billionths of a meter thick. That network could be the basis for a more efficient solar cell.

Solar Dreams

The crystalline-silicon solar cells that currently dominate the photovoltaic market are expensive—so expensive that the energy they produce costs several times as much as energy generated by fossil fuels. One reason is the high price of their raw materials. Silicon is extremely abundant on earth, but it doesn't exist as a pure element; instead, it's bound up with oxygen and other elements—in sand, for example. Making pure silicon requires a lot of energy.

To lower the costs of solar cells, researchers have looked for ways to cut down on the amount of silicon they use. Some have turned to less expensive thin films made from cadmium telluride or copper indium diselenide. Extremely thin layers of these new semiconductors can absorb the same amount of light as thicker slabs of crystalline silicon. Morse's fabrication technique could be an inexpensive way to make such thin films; in addition, the nanostructure that his method produces is particularly well suited for absorbing light and converting it into power.

A challenge in designing solar cells is making sure that the electrons dislodged when light hits a semiconductor create a current. When a photon strikes a solar-cell material, the result is both a free electron and its positive counterpart, called a hole. If these can be pulled apart quickly to opposite electrodes, an electrical current results. However, the difficulty of separating them before they recombine and dissipate energy as heat is "one of the major roadblocks for higher-efficiency solar cells," says Aravinda Kini, program manager for biomolecular materials research at the U.S. Department of Energy.

Morse's structures could surmount this roadblock. The network of crystalline projections could be immersed in a transparent solid or liquid electrode. Light would pass through the electrode, where it would be absorbed by the crystal. Because the surface area of the structured thin film is high (in one material, 90 to 100 times that of a traditional thin film), many of the electron-hole pairs generated by the light would be near the electrode interface; as a result, they could quickly separate, with one charge carrier moving into the transparent electrode and the other carrier traveling through the crystal to exit at the opposite electrode.

Already, Morse and colleagues have made more than 30 types of semiconductor thin films and tested their photovoltaic properties. They are now working to incorporate the semiconductors into functional solar cells. At the same time, Morse continues to develop new biologically inspired methods for assembling materials, with an eye to additional applications, including semiconductor devices for safer, higher-power-density batteries and smaller memory chips; he is also interested in creating laminated fibers for ultrastrong building materials.

But excited though he is by the potential applications of his work, Morse remains at heart a molecular biologist. Even as he talks about how his research could lead to better solar cells, he gazes out the window at the dolphins frolicking in the harbor. And he's still devoted to understanding the mechanism behind the complexity of the sponge. Once again he examines the exquisite skeleton of the Venus's flower basket, though he's no doubt seen it thousands of times. "This was made of glass, by a living creature," he exclaims. "It's incredible!" TR

Kevin Bullis is Technology Review*'s nanotechnology and materials science editor.*

Others in Bio-Inspired Materials

Researcher	Goal	Strategy
Joanna Aizenberg, Lucent Technologies, Murray Hill, NJ	Strong, self-healing building materials and more-resilient optical fibers	Understanding how sponges assemble inorganic materials
Illhan Aksay, Princeton University	Self-healing materials and better biosensors	Investigating seashells and other biological systems
Angela Belcher, MIT	Better batteries and advanced materials for electronics, energy, and medicine	Engineering viruses to assemble materials
Samuel I. Stupp, Northwestern University	Better sensors and solar cells	Using peptides to direct the formation of inorganic structures

Essay

A Failure of Intelligence

Operational research at RAF Bomber Command, 1943–1945

By Freeman Dyson

I began work in the Operational Research Section (ORS) of the British Royal Air Force's Bomber Command on July 25, 1943. I was 19 years old, fresh from an abbreviated two years as a student at the University of Cambridge.¶ The headquarters of Bomber Command was a substantial set of red brick buildings, hidden in the middle of a forest on top of a hill in the English county of Buckinghamshire. The main buildings had been built before the War. The ORS was added in 1941 and was housed in a collection of trailers at the back. Trees were growing right up to our windows, so we had little daylight even in summer. The Germans must have known where we were, but their planes never came to disturb us.

I was billeted in the home of the Parsons family in the village of Hughenden. Mrs. Parsons was a motherly soul and took good care of me. Once a week, she put her round tin bathtub out on her kitchen floor and filled it with hot water for my weekly splash. Each morning I bicycled the five miles up the hill to Bomber Command, and each evening I came coasting down. Sometimes, as I was struggling up the hill, an air force limousine would zoom by, and I would have a quick glimpse of our commander in chief, Sir Arthur Harris, sitting in the back, on his way to give the orders that sent thousands of boys my age to their deaths. Every day, depending on the weather and the readiness of the bombers, he would decide whether to send their crews out that night or let them rest. Every day, he chose the targets for the night.

"Bomber" Harris's entire career had been devoted to the proposition that strategic bombing could defeat Germany without the use of land armies. The mammoth force of heavy bombers that he commanded had been planned by the British government in 1936 as our primary instrument for defeating Hitler without repeating the horrors of the trench warfare of World War I. Bomber Command, by itself, was absorbing about one-quarter of the entire British war effort.

The members of Bomber Command's ORS were civilians, employed by the Ministry of Aircraft Production and not by the air force. The idea was that we would provide senior officers with independent scientific and technical advice. The experimental physicist Patrick Blackett had invented the ORS system in order to give advice to the navy. One of the crucial problems for the navy was to verify scientifically the destruction of U-boats. Every ship or airplane that dropped a depth charge somewhere near a U-boat was apt to claim a kill. An independent group of scientists was needed to evaluate the evidence impartially and find out which tactics were effective.

Bomber Command had a similar problem in evaluating the effectiveness of bombing. Aircrew frequently reported the destruction of targets when photographs showed they had missed by several miles. The navy ORS was extremely effective and made great contributions to winning the war against the U-boats in the Atlantic. But Blackett had two enormous advantages. First, he was a world-renowned scientist (who would later win a Nobel Prize), with a safe job in the academic world, so he could threaten to resign if his advice was not followed. Second, he had been a navy officer in World War I and was respected by the admi-

IMPERIAL WAR MUSEUM C3971

AIR WAR A British Lancaster bomber is silhouetted against flares and explosions during the attack on Hamburg, Germany, on the night of January 30, 1943.

rals he advised. Basil Dickins, the chief of our ORS at Bomber Command, had neither of these advantages. He was a civil servant with no independent standing. He could not threaten to resign, and Sir Arthur Harris had no respect for him. His career depended on telling Sir Arthur things that Sir Arthur wanted to hear. So that is what he did. He gave Sir Arthur information rather than advice. He never raised serious questions about Sir Arthur's tactics and strategy.

Our ORS was divided into sections and subsections. The sections were ORS1, concerned with bombing effectiveness; ORS2, concerned with bomber losses; ORS3, concerned with history. My boss, Reuben Smeed, was chief of ORS2. The subsections of ORS2 were ORS2a, collecting crew reports and investigating causes of losses; ORS2b, studying the effectiveness of electronic countermeasures; ORS2c, studying damage to returning bombers; ORS2d, doing statistical analysis and other jobs requiring some mathematical skill. I was put into ORS2d.

Two other new boys arrived at the same time I did. One was John Carthy, who was in ORS1; the other was Mike O'Loughlin, who shared an office with me in ORS2d. John had been a leading actor in the Cambridge University student theater. Mike had been briefly in the army but was discharged when he was found to be epileptic. John and Mike and I became lifelong friends. John was cheerful, Mike was bitter, and I was somewhere in between. In later life, John was a biologist at the University of London, and Mike taught engineering at the Cambridge Polytechnic. After retiring from the Polytechnic, Mike became an Anglican minister in the parish of Linton, near Cambridge.

The ORS consisted of about 30 people, a mixed bunch of civil servants, academic experts, and students. Working with us were an equal number of WAAFs, girls of the Women's Auxiliary Air Force, who wore blue uniforms and were subject to military discipline. The WAAFs were photographic interpreters, calculators, technicians, drivers, and secretaries. They did most of the real work of the ORS. They also supplied us with tea and sympathy. They made a depressing situation bearable. Their leader was Sergeant Asplen, a tall and strikingly beautiful girl whose authority was never questioned. The sergeant kept herself free of romantic entanglements. But two of her charges, a vivacious redhead named Dorothy and a more thoughtful brunette called Betty, became attached to my friends John and Mike. Love affairs were not officially discouraged. We celebrated two weddings before the War was over, with Dorothy and Betty discarding their dumpy blue uniforms for an afternoon and appearing resplendent in white silk. The marriages endured, and each afterwards produced four children.

My first day of work was the day after one of our most successful operations, a full-force night attack on Hamburg. For the first time, the bombers had used the decoy system, which we called WINDOW and the Americans called CHAFF. WINDOW consisted of packets of paper strips coated with aluminum paint. One crew member in each bomber was responsible for throwing packets of WINDOW down a chute, at a rate of one packet per minute, while flying over Ger-

COUNTERMEASURES A factory worker (this page) makes foil, code-named WINDOW, that was dropped by Allied aircraft to jam enemy radar. A Lancaster (opposite) sheds WINDOW in a daylight raid over Duisberg, Germany, in October 1944.

many. The paper strips floated slowly down through the stream of bombers, each strip a resonant antenna tuned to the frequency of the German radars. The purpose was to confuse the radars so that they could not track individual bombers in the clutter of echoes from the WINDOW.

That day, the people at the ORS were joyful. I never saw them as joyful again until the day that the war in Europe ended. WINDOW had worked. The bomber losses the night before were only 12 out of 791, or 1.5 percent, far fewer than would have been expected for a major operation in July, when the skies in northern Europe are never really dark. Losses were usually about 5 percent and were mostly due to German night fighters, guided to the bombers by radars on the ground. WINDOW had cut the expected losses by two-thirds. Each bomber carried a crew of seven, so WINDOW that night had saved the lives of about 180 of our boys.

The first job that Reuben Smeed gave me to do when I arrived was to draw pictures of the cloud of WINDOW trailing through the stream of bombers as the night progressed, taking into account the local winds at various altitudes as measured and reported by the bombers. My pictures would be shown to the aircrew to impress on them how important it was for them to stay within the stream after bombing the target, rather than flying home independently.

Smeed explained to me that the same principles applied to bombers flying at night over Germany and to ships crossing the Atlantic. Ships had to travel in convoys, because the risk of being torpedoed by a U-boat was much greater for a ship traveling alone. For the same reason, bombers had to travel in streams: the risk of being tracked by radar and shot down by an enemy fighter was much greater for a bomber flying alone. But the crews tried to keep out of the bomber stream, because they were more afraid of collisions than of fighters. Every time they flew in the stream, they would see bombers coming close and almost colliding with them, but they almost never saw fighters. The German night fighter force was tiny compared with Bomber Command. But the German pilots were highly skilled, and they hardly ever got shot down. They carried a firing system called Schräge Musik, or "crooked music," which allowed them to fly underneath a bomber and fire guns upward at a 60-degree angle. The fighter could see the bomber clearly silhouetted against the night sky, while the bomber could not see the fighter. This system efficiently destroyed thousands of bombers, and we did not even know that it existed. This was the greatest failure of the ORS. We learned about Schräge Musik too late to do anything to counter it.

Smeed believed the crew's judgement was wrong. He thought a bomber's chance of being shot down by a fighter was far greater than its chance of colliding with another bomber, even in the densest part of the bomber stream. But he had no evidence: he had

been too busy with other urgent problems to collect any. He told me that the most useful thing I could do was to become Bomber Command's expert on collisions. When not otherwise employed, I should collect all the scraps of evidence I could find about fatal and nonfatal collisions and put them all together. Then perhaps we could convince the aircrew that they were really safer staying in the stream.

There were two possible ways to study collisions, using theory or using observations. I tried both. The theoretical way was to use a formula: collision rate for a bomber flying in the stream equals density of bombers multiplied by average relative velocity of two bombers multiplied by mutual presentation area (MPA). The MPA was the area in a geometric plane perpendicular to the relative velocity within which a collision could occur. It was the same thing that atomic and particle physicists call a collision cross section. For vertical collisions, it was roughly four times the area of a bomber as seen from above. The formula assumes that two bombers on a collision course do not see each other in time to break off. For bombers flying at night over Germany, that assumption was probably true.

All three factors in the collision formula were uncertain. The MPA would be smaller for a sideways collision than for an up-and-down collision, but I assumed that most of the collisions would be

up-and-down, with the relative velocity vertical. The relative velocity would depend on how vigorously the bombers were corkscrewing as they flew. Except during bombing runs over a target, they never flew straight and level; that would have left them sitting ducks for antiaircraft guns. The standard maneuver for avoiding antiaircraft fire was the corkscrew, combining side-to-side with up-and-down weaving. For predicting collisions, it was the up-and-down motion that was most important. From crew reports I estimated up-and-down motions averaging 40 miles an hour, uncertain by a factor of two. But the dominant uncertainty in the collision formula was the density of bombers in the stream.

I studied the crew reports, which sometimes described large deviations from the tracks that the bombers were supposed to fly. For the majority of crews, who reported no large deviations, there was no way to tell how close to their assigned tracks they actually flew. My best estimate of the density of bombers was uncertain by a factor of 10. This made the collision formula practically worthless as a predictive tool. But it still had value as a way to set an upper bound on the collision rate. If I assumed maximum values for all three factors in the formula, it gave a loss rate due to collisions of 1 percent per operation. One percent was much too high to be acceptable, but still less than the overall loss rate of 5 percent. Even if we squeezed the bomber stream to the highest possible density, collisions would not be the main cause of losses.

How common, really, were collisions? Observational evidence of lethal crashes over Germany was plentiful but unreliable. The crews frequently reported seeing events that *looked* like collisions: first an explosion in the air, and then two flaming objects falling to the ground. These events were visible from great distances and were often multiply reported. The crews tended to believe that they were seeing collisions, but there was no way to be sure. Most of the events probably involved single bombers, hit by antiaircraft shells or by fighter cannon fire, that broke in half as they disintegrated.

In the end I found only two sources of evidence that I could trust: bombers that collided over England and bombers that returned damaged by nonlethal collisions over Germany. The numbers of incidents of both kinds were reliable, and small enough that I could investigate each case individually. The case that I remember best was a collision between two Mosquito bombers over Munich. The Mosquito was a light, two-seat bomber that Bomber Command used extensively for small-scale attacks, to confuse the German defenses and distract attention from the heavy attacks. Two Mosquitoes flew alone from England to Munich and then collided over the target, with only minor damage. It was obvious that the collision could not have been the result of normal operations. The two pilots must have seen each other when they got to Munich and started playing games. The Mosquito was fast and maneuverable and hardly ever got shot down, so the pilots felt themselves to be invulnerable. I interviewed Pilot-Officer Izatt, who was one of the two pilots. When I gently questioned him about the Munich operation, he confessed that he and his friend had been enjoying a dogfight over the target when they bumped into each other. So I crossed the Munich collision off my list. It was not relevant to the statistics on collisions between heavy bombers in the bomber stream. There remained seven authentic nonlethal collisions between heavy bombers over Germany.

For bombers flying at night over England in training exercises, I knew the numbers of lethal and nonlethal collisions. After more than 60 years, I can't recall them precisely, but I remember that the ratio of lethal to nonlethal collisions was three to one. If I assumed that the chance of surviving a collision was the same over Germany as over England, then it was simple to calculate the number of lethal collisions over Germany. But there were two reasons that assumption might be false. On the one hand, a badly damaged aircraft over Germany might fail to get home, while an aircraft with the same damage over England could make a safe landing. On the other hand, the crew of a damaged aircraft over England might decide to bail out and let the plane crash, while the same crew over Germany would be strongly motivated to bring the plane home. There was no way to incorporate these distinctions into my calculations. But since they pulled in opposite directions, I decided to ignore them both. I estimated the number of lethal collisions over Germany in the time since the massive attacks began to be three times the number of nonlethal collisions, or 21. These numbers referred to major operations over Germany with high-density bomber streams, in which about 60,000 sorties had been flown at the time I did the calculation. So collisions destroyed 42 aircraft in 60,000 sorties, a loss rate of .07 percent. This was the best estimate I could make. I could not calculate any reliable limits of error, but I felt confident that the estimate was correct within a factor of two. It was consistent with the less accurate estimate obtained from the theoretical formula, and it strongly confirmed Smeed's belief that collisions were a smaller risk than fighters.

For a week after I arrived at the ORS, the attacks on Hamburg continued. The second, on July 27, raised a firestorm that devastated the central part of the city and killed about 40,000 people. We succeeded in raising firestorms only twice, once in Hamburg and once more in Dresden in 1945, where between 25,000 and 60,000 people perished (the numbers are still debated). The Germans had good air raid shelters and warning systems and did what they were told. As a result, only a few thousand people were killed in a typical major attack. But when there was a firestorm, people were asphyxiated or roasted inside their shelters, and the number killed was more than 10 times greater. Every time Bomber Command attacked a city, we were trying to raise a firestorm, but we never learnt why we so seldom succeeded. Probably a firestorm could happen only when three things occurred together: first, a high concentration of old buildings at the target site; second, an attack with a high density of incendiary bombs in the target's central area; and, third, an atmospheric instability. When the combination of these three things was just right, the flames and the winds produced a blazing hurricane. The same thing happened one night in Tokyo in March 1945 and once more at Hiroshima the following August. The Tokyo firestorm was the biggest, killing perhaps 100,000 people.

The third Hamburg raid was on the night of July 29, and the fourth on August 2. After the firestorm, the law of diminishing returns was operating. The fourth attack was a fiasco, with high and heavy clouds over the city and bombs scattered over the countryside. Our bomber losses were rising, close to 4 percent for the third attack and a little over 4 percent for the fourth. The Germans had learnt quickly how to deal with WINDOW. Since they could no longer track individual bombers with radar, they guided their fighters into the bomber stream and let them find their own targets. Within a month, loss rates were back at the 5 percent level, and WINDOW was no longer saving lives.

Another job that Smeed gave me was to invent ways to estimate the effectiveness of various countermeasures, using all the evidence from a heterogeneous collection of operations. The first countermeasure that I worked on was MONICA. MONICA was a tail-mounted warning radar that emitted a high-pitched squeal over the intercom when a bomber had another aircraft close behind it. The squeals came more rapidly as the distance measured by the radar became shorter. The crews disliked MONICA because it was too sensitive and raised many false alarms. They usually switched it off so that they could talk to each other without interruption. My job was to see from the results of many operations whether MONICA actually saved lives. I had to compare the loss rates of bombers with and without MONICA. This was difficult because MONICA was distributed unevenly among the squadrons. It was given preferentially to Halifaxes (one of the two main types of British heavy bomber), which usually had higher loss rates, and less often to Lancaster bombers, which usually had lower loss rates. In addition, Halifaxes were sent preferentially on less dangerous operations and Lancasters on more dangerous operations. To use all the evidence from Halifax and Lancaster losses on a variety of operations, I invented a method that was later reinvented by epidemiologists and given the name "meta-analysis." Assembling the evidence from many operations to judge the effectiveness of MONICA was just like assembling the evidence from many clinical trials to judge the effectiveness of a drug.

My method of meta-analysis was the following: First, I subdivided the data by operation and by type of aircraft. For example, one subdivision would be Halifaxes on Bremen on March 5; another would be Lancasters on Berlin on December 2. In each subdivision I tabulated the number of aircraft with and without MONICA and the number lost with and without MONICA. I also tabulated the number of MONICA aircraft expected to be lost if the warning system had no effect, and the statistical variance of that number. So I had two quantities for each subdivision: observed-minus-expected losses of MONICA aircraft, and the variance of this difference. I assumed that the distributions of losses in the various subdivisions were uncorrelated. Thus, I could simply add up the two quantities, observed-minus-expected losses and variance, over all the subdivisions. The result was a total observed-

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HIVE MIND Air Marshal Sir Richard Peirse, who preceded Sir Arthur Harris as commander in chief, Bomber Command, leads the planning of a night's operations in the Operations Room at headquarters, RAF Bomber Command.

minus-expected losses and variance for all the MONICA aircraft, unbiased by the different fractions of MONICA aircraft in the various subdivisions. This was a sensitive test of effectiveness, making use of all the available information. If the total of observed-minus-expected losses was significantly negative, it meant that MONICA was effective. But instead, the total was slightly positive and less than the square root of the total variance. MONICA was statistically worthless. The crews had been right when they decided to switch it off.

I later applied the same method of analysis to the question of whether experience helped crews to survive. Bomber Command told the crews that their chances of survival would increase with experience, and the crews believed it. They were told, *After you have got through the first few operations, things will get better.* This idea was important for morale at a time when the fraction of crews surviving to the end of a 30-operation tour was only about 25 percent. I subdivided the experienced and inexperienced crews on each operation and did the analysis, and again, the result was clear. Experience did not reduce loss rates. The cause of losses, whatever it was, killed novice and expert crews impartially. This result contradicted the official dogma, and the Command never accepted it. I blame the ORS, and I blame myself in particular, for not taking this result seriously enough. The evidence showed that the main cause of losses was an attack that gave experienced crews no chance either to escape or to defend themselves. If we had taken the evidence more seriously, we might have discovered Schräge Musik in time to respond with effective countermeasures.

Smeed and I agreed that Bomber Command could substantially reduce losses by ripping out two gun turrets, with all their associated hardware, from each bomber and reducing each crew from seven to five. The gun turrets were costly in aerodynamic drag as well as in weight. The turretless bombers would have flown 50 miles an hour faster and would have spent much less time over Germany. The evidence that experience did not reduce losses confirmed our opinion that the turrets were useless. The turrets did not save bombers, because the gunners rarely saw the fighters that killed them. But our proposal to rip out the turrets went against the official mythology of the gallant gunners defending their crewmates. Dickins never had the courage to push the issue seriously in his conversations with Harris. If he had, Harris might even have listened, and thousands of crewmen might have been saved.

The part of his job that Smeed enjoyed most was interviewing evaders. Evaders were crew members who had survived being shot down over German-occupied countries and made their way back to England. About 1 percent of all those shot down came back. Each week, Smeed would go to London and interview one or two of them. Sometimes he would take me along. We were not supposed to ask them questions about how they got back, but they would sometimes tell us amazing stories anyway. We were *supposed* to ask them questions about how they were shot down. But they had very little information to give us about that. Most of them said they never saw a fighter and had no warning of an attack. There was just a sudden burst of cannon fire, and the aircraft fell apart around them. Again, we missed an essential clue that might have led us to Schräge Musik.

IMPERIAL WAR MUSEUM CH3337

On November 18, 1943, Sir Arthur Harris started the Battle of Berlin. This was his last chance to prove the proposition that strategic bombing could win wars. He announced that the Battle of Berlin would knock Germany out of the War. In November 1943, Harris's bomber force was finally ready to do what it was designed to do: smash Hitler's empire by demolishing Berlin. The Battle of Berlin started with a success, like the first attack on Hamburg on July 24. We attacked Berlin with 444 bombers, and only 9 were lost. Our losses were small, not because of WINDOW, but because of clever tactics. Two bomber forces were out that night, one going to Berlin and one to Mannheim. The German controllers were confused and sent most of the fighters to Mannheim.

After that first attempt on Berlin, Sir Arthur ordered 15 more heavy attacks, expecting to destroy that city as thoroughly as he had destroyed Hamburg. All through the winter of 1943 and '44, the bombers hammered away at Berlin. The weather that winter was worse than usual, covering the city with cloud for weeks on end. Our photoreconnaissance planes could bring back no pictures to show how poorly we were doing. As the attacks went on, the German defenses grew stronger, our losses heavier, and the "scatter" of the bombs worse. We never raised a firestorm in Berlin. On March 24, in the last of the 16 attacks, we lost 72 out of 791 bombers, a loss rate of 9 percent, and Sir Arthur admitted defeat. The battle cost us 492 bombers with more than 3,000 aircrew. For all that, industrial production in Berlin continued to increase, and the operations of government were never seriously disrupted.

There were two main reasons why Germany won the Battle of Berlin. First, the city is more modern and less dense than Hamburg, spread out over an area as large as London with only half of London's population; so it did not burn well. Second, the repeated attacks along the same routes allowed the German fighters to find the bomber stream earlier and kill bombers more efficiently.

A week after the final attack on Berlin, we suffered an even more crushing defeat. We attacked Nuremberg with 795 bombers and lost 94, a loss rate of almost 12 percent. It was then clear to everybody that such losses were unsustainable. Sir Arthur reluctantly abandoned his dream of winning the War by himself. Bomber Command stopped flying so deep into Germany and spent the summer of 1944 giving tactical support to the Allied armies that were, by then, invading France.

The history of the 20th century has repeatedly shown that strategic bombing by itself does not win wars. If Britain had decided in 1936 to put its main effort into building ships instead of bombers, the invasion of France might have been possible in 1943 instead of 1944, and the war in Europe might have ended in 1944 instead of 1945. But in 1943, we had the bombers, and we did not have the ships, and the problem was to do the best we could with what we had.

One of our group of young students at the ORS was Sebastian Pease, known to his friends as Bas. He had joined the ORS only six months before I had, but by the time I got there, he already knew his way around and was at home in that alien world. He was the only one of us who was actually doing what we were all supposed to be doing: helping to win the War. The rest of us were sitting at Command Headquarters, depressed and miserable because our losses of aircraft and aircrew were tremendous and we were unable to do much to help. The Command did not like it when civilians wandered around operational squadrons collecting information, so we were mostly confined to our gloomy offices at the headquarters. But Bas succeeded in breaking out. He spent most of his time with the squadrons and came back to headquarters only occasionally. Fifty years later, when he was visiting Princeton (where I spent most of my life, working as a professor of physics), he told me what he had been doing.

Bas was able to escape from Command Headquarters because he was the expert in charge of a precise navigation system called G-H. Only a small number of bombers were fitted with G-H, because it required two-way communication with ground stations. These bombers belonged to two special squadrons, 218 Squadron being one of them. The G-H bombers were Stirlings, slow and ponderous machines that were due to be replaced by the smaller and more agile Lancasters. They did not take part in mass-bombing operations with the rest of the Command but did small, precise operations on their own with very low losses. Bas spent a lot of time at 218 Squadron and made sure that the G-H crews knew how to use their equipment to bomb accurately. He had "a good war," as we used to say in those days. The rest of us were having a bad war.

Sometime early in 1944, 218 Squadron stopped bombing and started training for a highly secret operation called GLIMMER, which Bas helped to plan, and whose purpose was to divert German attention from the invasion fleet that was to invade France in June. The operation was carried out on the night of June 5–6. The G-H bombers flew low, in tight circles, dropping WINDOW as they moved slowly out over the English Channel. In conjunction with boats below them that

carried specially designed radar transponders, they appeared to the German radars to be a fleet of ships. While the real invasion fleet was moving out toward Normandy, the fake invasion fleet of G-H bombers was moving out toward the Pas de Calais, 200 miles to the east. The ruse was successful, and the strong German forces in the Pas de Calais did not move to Normandy in time to stop the invasion. While Bas was training the crews, he said nothing about it to his friends at the ORS. We knew only that he was out at the squadrons doing something useful. Even when GLIMMER was over and the invasion had succeeded, Bas never spoke about it. My boss, Reuben Smeed, was a man of considerable wisdom. One day at Bomber Command, he said, "In this business, you have a choice. Either you get something done or you get the credit for it, but not both." Bas's work was a fine example of Smeed's dictum. He made his choice, and he got something done. In later life he became a famous plasma physicist and ran the Joint European Torus, the main fusion program of the European Union.

The one time that *I* did something practically useful for Bomber Command was in spring 1944, when Smeed sent me to make accurate measurements of the brightness of the night sky as a function of time, angle, and altitude. The measurements would be used by our route planners to minimize the exposure of bombers to the long summer twilight over Germany. I went to an airfield at the village of Shawbury in Shropshire and flew for several nights in an old Hudson aircraft, unheated and unpressurized. The pilot flew back and forth on a prescribed course at various altitudes, while I took readings of sky brightness through an open window with an antiquated photometer, starting soon after sunset and ending when the sun was 18 degrees below the horizon. I was surprised to find that I could function quite well without oxygen at 20,000 feet. I shared this job with J. F. Cox, a Belgian professor who was caught in England when Hitler overran Belgium in 1940. Cox and I took turns doing the measurements. My flights were uneventful, but on the last of Cox's flights, both of the Hudson's engines failed, and the pilot decided to bail out. Cox also bailed out and came to earth still carrying the photometer. He broke an ankle but saved the device. In later years, he became rector of the Free University in Brussels.

> The British mostly supported Sir Arthur's ruthless bombing of cities, not because they believed that it was militarily necessary, but because they felt it was teaching German civilians a good lesson.

After the War, Smeed worked for the British government on road traffic problems and then taught at University College London, where he was the first professor of traffic studies. He applied the methods of operational research to traffic problems all over the world and designed intelligent traffic-light control systems to optimize the flow of traffic through cities. Smeed had a fatalistic view of traffic flow. He said that the average speed of traffic in central London would always be nine miles per hour, because that is the minimum speed that people will tolerate. Intelligent use of traffic lights might increase the number of cars on the roads but would not increase their speed. As soon as the traffic flowed faster, more drivers would come to slow it down.

Smeed also had a fatalistic view of traffic accidents. He collected statistics on traffic deaths from many countries, all the way back to the invention of the automobile. He found that under an enormous range of conditions, the number of deaths in a country per year is given by a simple formula: number of deaths equals .0003 times the two-thirds power of the number of people times the one-third power of the number of cars. This formula is known as Smeed's Law. He published it in 1949, and it is still valid 57 years later. It is, of course, not exact, but it holds within a factor of two for almost all countries at almost all times. It is remarkable that the number of deaths does not depend strongly on the size of the country, the quality of the roads, the rules and regulations governing traffic, or the safety equipment installed in cars. Smeed interpreted his law as a law of human nature. The number of deaths is determined mainly by psychological factors that are independent of material circumstances. People will drive recklessly until the number of deaths reaches the maximum they can tolerate. When the number exceeds that limit, they drive more carefully. Smeed's Law merely defines the number of deaths that we find psychologically tolerable.

The last year of the War was quiet at ORS Bomber Command. We knew that the War was coming to an end and that nothing we could do would make much difference. With or without our help, Bomber Command was doing better. In the fall of 1944, when the Germans were driven out of France, it finally became possible for our bombers to make accurate and dev-

EFFECTS The ruins of Hamburg after Allied bombing in July 1943

KEYSTONE/GETTY IMAGES

astating night attacks on German oil refineries and synthetic-oil-production plants. We had long known these targets to be crucial to Germany's war economy, but we had never been able to attack them effectively. That changed for two reasons. First, the loss of France made the German fighter defenses much less effective. Second, a new method of organizing attacks was invented by 5 Group, the most independent of the Bomber Command groups. The method originated with 617 Squadron, one of the 5 Group squadrons, which carried out the famous attack on the Ruhr dams in March 1943. The good idea, as usually happens in large organizations, percolated up from the bottom rather than trickling down from the top. The approach called for a "master bomber" who would fly a Mosquito at low altitude over a target, directing the attack by radio in plain language. The master bomber would first mark the target accurately with target indicator flares and then tell the heavy bombers overhead precisely where to aim. A deputy master bomber in another Mosquito was ready to take over in case the first one was shot down. Five Group carried out many such precision attacks with great success and low losses, while the other groups flew to other places and distracted the fighter defenses. In the last winter of the War, the German army and air force finally began to run out of oil. Bomber Command could justly claim to have helped the Allied armies who were fighting their way into Germany from east and west.

While the attacks on oil plants were helping to win the War, Sir Arthur continued to order major attacks on cities, including the attack on Dresden on the night of February 13, 1945. The Dresden attack became famous because it caused a firestorm and killed a large number of civilians, many of them refugees fleeing from the Russian armies that were overrunning Pomerania and Silesia. It caused some people in Britain to question the morality of continuing the wholesale slaughter of civilian populations when the War was almost over. Some of us were sickened by Sir Arthur's unrelenting ferocity. But our feelings of revulsion after the Dresden attack were not widely shared. The British public at that time still had bitter memories of World War I, when German armies brought untold misery and destruction to other people's countries, but German civilians never suffered the horrors of war in their own homes. The British mostly supported Sir Arthur's ruthless bombing of cities, not because they believed that it was militarily necessary, but because they felt it was teaching German civilians a good lesson. This time, the German civilians were finally feeling the pain of war on their own skins.

I remember arguing about the morality of city bombing with the wife of a senior air force officer, after we heard the results of the Dresden attack. She was a well-educated and intelligent woman who worked part-time for the ORS. I asked her whether she really believed that it was right to kill German women and babies in large numbers at that late stage of the War. She answered, "Oh yes. It is good to kill the babies especially. I am not thinking of this war but of the next one, 20 years from now. The next time the Germans start a war and we have to fight them, those babies will be the soldiers." After fighting Germans for ten years, four in the first war and six in the second, we had become almost as bloody-minded as Sir Arthur.

At last, at the end of April 1945, the order went out to the squadrons to stop offensive operations. Then the order went out to fill the bomb bays of our bombers with food packages to be delivered to the starving population of the Netherlands. I happened to be at one of the 3 Group bases at the time and watched the crews happily taking off on their last mission of the War, not to kill people but to feed them. TR

Freeman Dyson was for many years professor of physics at the Institute for Advanced Study in Princeton. He is famous for his contributions to mathematical physics, particularly for his work on quantum electrodynamics. He was awarded the Lorentz Medal in 1966 and the Max Planck Medal in 1969, both for his contributions to modern physics. In 2000, he was awarded the Templeton Prize for Progress in Religion.

Reviews

Books, artifacts, reports, products, objects

POPULAR CULTURE

Fakesters

On MySpace, you can be friends with Burger King. This is social networking? **By Wade Roush**

Web users have created more than 116 million profiles on MySpace, the social-networking site owned since 2005 by Rupert Murdoch's News Corp. As I will explain in a moment, many of these profiles are fake. Still, 116 million is more than the number of people in Mexico and the number of cable TV subscribers in the United States.

Parents and members of the U.S. Congress have begun to take note—and they don't like what they see. Conservative groups fomented a media panic this year over the supposed rash of sexual predators on MySpace and pushed a bill through the House of Representatives—the Delete Online Predators Act (DOPA)—that would cut off minors' ability to access this and other social-networking sites from federally funded facilities like schools and libraries.

MYSPACE
Author's profile:
www.myspace.com/wroush

In the opinion of experts such as Henry Jenkins, a professor of literature and director of the Comparative Media Studies Program at MIT, the threat of sexual solicitation on MySpace is not as great as many fear. The company has indeed been hit with a high-profile lawsuit over an incident in which an adult molester allegedly met his underage victim on the site. But teens who use the Internet have said in surveys that online "solicitations" often come from people under 25—and are simply ignored. Furthermore, MySpace is likely to get safer: an October Wired News report that as many as 744 registered sex offenders have MySpace profiles will likely push the company to cull such members.

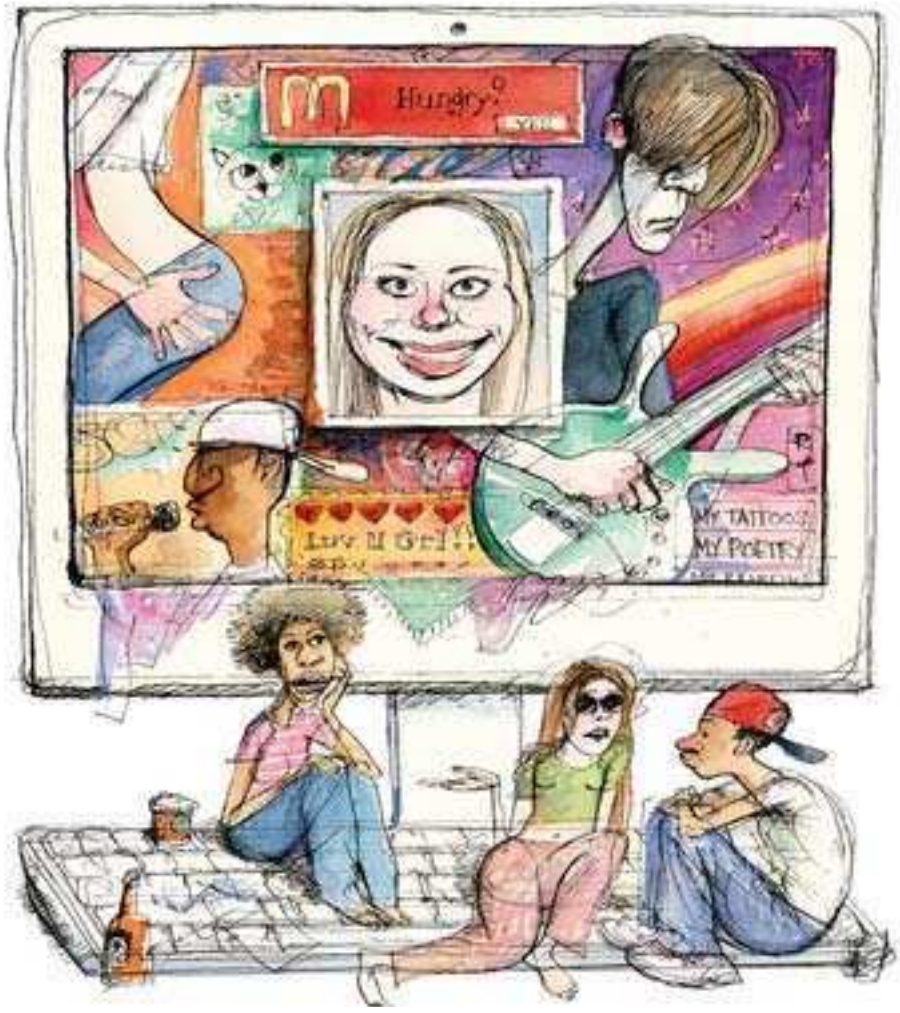
But while MySpace's bad rap as a haven for sexual predators is probably undeserved, there's good reason to be disturbed by the site: it is devolving from a friends' network into a marketing madhouse.

If any social-networking company has found a way to rake in cash, it is MySpace; for example, Google recently agreed to pay $900 million for the exclusive right to provide Web searching and keyword-based text ads on the site. Of course, targeted advertisements distributed by Google and other companies provide the revenue that keeps many Web-based businesses afloat. But MySpace's venture into consumer marketing has gone far beyond traditional advertising. The site has given members the technological tools to "express themselves" by turning their own profiles into multimedia billboards for bands, movies, celebrities, and products. Think MTV plus user photos, bulletin boards, and instant messaging.

I realize that in criticizing a pop-culture mecca frequented by millions of people, I risk sounding just as out of touch as DOPA's supporters. But after spending the last few years chronicling the emergence of social networking and other forms of social computing for this magazine, I had higher hopes for the technology. To me, the popularity of MySpace and other social-networking sites signals a demand for new, more democratic ways to communicate—a demand that's likely to remake business, politics, and the arts as today's young Web users enter the adult world and bring their new communications preferences with them. The problem is that MySpace's choice of business strategy threatens to divert this populist energy and trap its users in the old, familiar world of big-media commercialism.

My biggest worry about MySpace is that it is undermining the "social" in social networking. The general expectation when one joins a social network is that its other members are actual people. On MySpace, this isn't always so. The movie *Jackass: Number Two* has a profile on the site, as do Pepsi, NASCAR, and Veronica Mars, the CW network's teen detective. The company interprets the idea of a "profile" so broadly that real people end up on the same footing as products, movies, promotional campaigns, and fictional characters—not exactly the conditions for a new flowering of authentic personal expression.

As a site organized around an enormous collection of profiles, MySpace was modeled on Friendster and other earlier online social networks. Users are given pages where they can post self-descriptions, photos, short videos, blog entries, and the like. Every profile



RICHARD THOMPSON

includes a list of the other members its creator has "friended," and a comment section where those friends leave feedback. (Most comments are encouraging, casual, and shallow: "Love the new look! How are you not married yet?")

But one feature that makes MySpace different from earlier sites, and evidently more appealing to users, is its friendliness toward independent artists. Cofounder Tom Anderson, who has a background in the Los Angeles arts scene, has said that he and business partner Chris DeWolfe started the site in 2003 because the older social networks didn't give musicians, photographers, digital filmmakers, and other artists adequate ways to promote themselves and their work. From its beginning, then, MySpace has functioned as a public stage. It lets bands and solo musicians create profiles, publicize upcoming shows, and upload their songs, which other members can then embed in their own profiles. Filmmakers can upload video clips. Indeed, the site has become one of the main places where unknown artists go to be discovered by major studios, or at least to develop a base of fans who'll attend shows and buy CDs and DVDs.

In the early days at Friendster, only real individuals could create profiles. Bands were lumped in with other "fakesters," the term coined by Friendster users for profiles created by impostors or dedicated to someone other than the author, such as a pet or a celebrity. The company eventually relented, and fakester profiles became an accepted part of Friendster's culture, often taking on the function of fan clubs.

MySpace, however, has been hospitable to fakesters from the beginning—so much so that it's now perfectly kosher for a company (or one of its fans) to create a profile for a fast-food chain, a brand of soda, or an electronics product. Other MySpace members can friend these profiles just as if they represented people. As of early October, Burger King had more than 134,500 friends, and the Helio cell phone had 130,000.

The fakester phenomenon gives network members a way to declare their cultural affinities. These declarations are a huge part of a member's online identity, according to social-media researcher Danah Boyd, who is studying MySpace and other social-networking sites for her doctoral thesis at the University of California, Berkeley's School of Information. "It is important to be connected to all of your friends, your idols and the people you respect," Boyd writes. "Of course, a link does not necessarily mean a relationship ….The goal is to look cool and receive peer validation."

But profiles are about more than looking cool, in Boyd's view. She argues that social-networking sites are among the last unregimented environments for young people, places where they're free to explore issues of personal and group identity. Members of such sites "write themselves into being" through their profiles, Boyd says, trying out personalities and slowly coming to understand who they are and how they fit in.

Ideally, every networking site would be this liberating. Alas, MySpace tends to herd its users into niches created for them by the mass market. If MySpace members are writing themselves into being through the profiles they friend and the products they endorse, then today's 14-to-24-year-olds are growing up into a generation of Whopper-eating, iPod-absorbed, Hollywood-obsessed Red Bull addicts.

Take BillyJ (not his real handle), an 18-year-old high-school graduate and UPS employee in Louisville, KY. BillyJ smokes Kools, prefers Coke to Pepsi, counts *X-Men: The Last Stand*

among his 393 friends, admires New Jersey Nets guard Jason Kidd, likes to work on car audio systems, doesn't have a girlfriend yet, and apparently covets a Ducati motorcycle (his profile features customized Ducati backgrounds, color schemes, and ads). BillyJ may have deeper, more personal interests, but you won't find them on his MySpace profile. It's unclear what he contributes to the network—but as a single 18-to-24-year-old male with his own income and lots of friends, he is a viral marketer's dream vector.

In fact, MySpace can be viewed as one huge platform for "personal product placement"—one different from big-media-style product placement only in that MySpace members aren't paid for their services. There's nothing new, of course, about word-of-mouth marketing. What's sad about MySpace, though, is that the large supply of fake "friends," together with the cornucopia of ready-made songs, videos, and other marketing materials that can be directly embedded in profiles, encourages members to define themselves and their relationships almost solely in terms of media and consumption.

This can't be all that social computing has to offer. Older Web-based social networks were launched with serious (or at least creative) missions: LinkedIn is about making business connections, Flickr and Fotolog are for sharing photographs, Meetup is for planning book clubs and campaign events. Of course, there's no requirement that a social network have high ideals. Like television and every other technology that started out as a shiny showroom prototype, social networking will inevitably accumulate some dings and scratches on the road to mass adoption. But if MySpace is to be the face of online social networking, it's fair to ask whether it's making our culture richer or poorer. To date, the only people who are profiting are Rupert Murdoch and his stockholders. TR

Wade Roush is a Technology Review *contributing editor.*

(HIGHLY) PERSONAL TECHNOLOGY

Spying On My Wife

Surveillance gizmos are a part of my life. What do they reveal?

By Simson Garfinkel

My wife was fine, but her 2005 Honda Pilot was totaled. On Interstate 95 between New Haven and Boston, the SUV had been picked up by the wind from a passing 18-wheeler and hurled against the median strip. My wife told me she wasn't speeding, but I didn't really believe her. So I bought a CarChip and (with her permission) installed it in our family's other SUV, a 1996 Jeep Cherokee. Now I know if she's been speeding or not—and a whole lot more.

CARCHIP E/X
Davis Instruments
$179

The CarChip is a 35-by-48-by-25-millimeter data recorder that plugs into a connector found under the dashboard of most cars and light trucks sold in the United States and Canada since 1996. The connector lets the CarChip continuously record data, such as speed and acceleration, fed to it by the car's onboard diagnostics system. To get the data out of the chip, you just unplug it, attach it to a Windows-based computer, and run a downloader program.

The CarChip's reports contain an incredible amount of data. The report for each trip notes when the engine was started, when it stopped, and how fast the car was going every five seconds in between—all in the form of a pretty graph. The graph is annotated with warning lines that show excessive speed, as determined by the user (my settings are for 70 miles per hour), as well as incidents of sudden braking and acceleration. You can feed the data into a spreadsheet, and if you buy enough chips and special software, you can maintain records for all the cars in your family or corporate fleet.

Davis Instruments makes three versions of the CarChip. The basic chip holds 75 hours of data and costs $139. I bought the CarChip E/X, which holds 300 hours of data, can monitor any 4 of 23 engine parameters (including such geeky things as the oxygen sensor voltage and the engine load), and has an "accident log" that stores the speed of the car for the last 20 seconds before a crash. The E/X costs $179. Finally, for $199, the CarChip E/X with Alarm allows you to set alarms for excessive speed, hard braking, or sudden acceleration. This device is designed to deliver an audible warning when drivers are engaging in risky behavior.

But as any scientist will tell you, it's one thing to collect data and another thing to understand what the data actually mean. In the case of the CarChip, understanding requires a deep knowledge of the car's driver and her habits.

One evening two months after I installed the CarChip, I suggested to my wife that we light some candles, put on some soft music, gather at my computer, and review her driving record.

Although the CarChip records only how fast the car is moving, the patterns in my wife's daily routine made it easy for us to figure out where it had been traveling at which points on the graph. When the car starts at 8:50 A.M., drives three miles, and stops at 9:15 A.M., that's a pretty good indication that my wife has just taken our twins to school—and gotten there 15 minutes late. She does this with staggering regularity.

Then we discovered a 74-mile drive with several instances of travel over 70 miles per hour, two acts of sudden braking, and one act of very fast acceleration. And it was on a Sunday, when she was driving our daughter to camp. Whoops, actually I was driving that time. But you get the idea.

The CarChip is just one of a growing number of products that let us collect extraordinarily detailed data about the people we know and love—or work with. Memory chips are getting bigger, networks are becoming better connected, and sensors are becoming more accurate and affordable. And more and more products come with built-in tracking that's turned on by default. If you don't want your own belongings tracking your movements, it's up to you to find out what they're doing and make them stop.

For example, according to the National Highway Traffic Safety Administration, about 64 percent of the model 2005 cars sold in the United States were equipped with event data recorders (EDRs). Similar to the so-called black boxes in airplanes, these systems continuously monitor a variety of statistics and preserve their most recent readings if the vehicle crashes. According to the NHTSA, EDRs typically record "pre-crash vehicle dynamics and system status" (such as the car's speed), "driver inputs" (the position of the steering wheel and throttle and whether the brake is engaged), the "vehicle crash signature" (the car's change in velocity during a crash), and "restraint usage/deployment status" (how quickly the air bags were released). Consumers typically don't get access to this information. Its purpose, instead, is to help industry and the government make cars and roads safer. Increasingly, it is being used in the courtroom as well.

The problem with these EDRs is that most drivers don't know they're there. This creates the risk that the information will only be used against you. For example, the police might pull the data from your EDR if they think it will prove you were speeding, but intentionally neglect to pull it if there is an eyewitness to testify that you were. That's a problem, because observers who witness a messy crash might inadvertently exaggerate how fast a car was going. In two recently reported cases, EDRs have shown that cars were traveling slower than eyewitnesses thought.

The Electronic Privacy Information Center argued in 2004 that in addition to being informed about EDRs' presence, car owners should be allowed to control whether the devices collect information and how that information is disseminated. This year the NHTSA issued a rule requiring that EDRs be mentioned in owner's manuals and that they record a consistent set of data; but those rules won't go into effect until 2010.

Cell phones are another great source of personal data. Sprint's Family Locator service allows parents to see where

their cell-phone-carrying children (or spouses) are. The system can also record a phone's position at specified times or follow the phone and leave "bread crumbs" on an interactive map that's viewable over the Web or from a Web-enabled phone.

Even door locks can provide useful information for someone wanting details on the comings and goings of others. Not old-fashioned lock-and-key systems, that is, but "access control" systems based on codes, pass cards, or radio frequency identification (RFID). Years ago, for example, I had a biometric, voiceprint-based lock on the front door of my house in Cambridge, MA. Everybody had a unique code, of course, so I was able to use the system to see if my live-in girlfriend was coming home on nights when I was out of town. (She wasn't.)

All these data surveillance systems certainly prove themselves useful from time to time, and increasingly they're being used by parents and corporations to keep track of children and employees. I recently spoke with a computer forensics specialist who told me that he used the log of a card-key system to show convincingly that an employee suspected of visiting pornographic websites and trying to break in to corporate computers had actually been framed by someone in his company's IT support group. The attack happened at 2:00 A.M., when the employee was home in bed; the IT person often worked late.

Any monitoring system can be defeated, of course. A child who doesn't want her cell phone tracked can turn it off or "accidentally" leave it at a friend's house. I can wait at the front door of an office until it's opened by a coworker. And my wife can unplug her CarChip if she doesn't want to be tracked. The CarChip tries to defend itself against this ploy by recording the fact that it was unplugged and then plugged in again at a later time, but it can't tell you what happened in the interim.

That's why I think the real use of these systems isn't surveillance but self-knowledge. I want to know if I am routinely driving faster than the speed limit, or if I am gunning the engine and then hitting the brakes. That's why I ordered a CarChip for my little blue sports car. If I ever do get in an accident, I want to have proof that I wasn't at fault. Unless, of course, I was, in which case I expect this little Big Brother to get mysteriously lost in the confusion that follows. TR

Simson Garfinkel researches computer forensics at the Harvard Center for Research on Computation and Society.

JASON SCHNEIDER

PHARMACOGENOMICS

Still Waiting for Personalized Medicine

Pharmacogenomics promises to allow doctors to choose drugs and dosages based on tests of your genetic profile. But just try taking one of those tests. **By Emily Singer**

Nausea, fatigue, dizziness, dry mouth, insomnia. For people like me, who seem susceptible to every side effect possible, the tiny type on ads for new drugs is required reading. NyQuil puts me into a half-conscious delirium. Codeine makes me throw up. And back in college, when my doctor prescribed Wellbutrin to help me quit smoking, I experienced blurred vision and the worst headaches of my life.

Given that my troubled history with medication is shared by my mother and sister, I have long suspected a genetic basis for my sensitivity. So like many others, I have over the last few years eagerly anticipated the benefits of pharmacogenomics—a field whose researchers aim to let doctors tailor prescriptions to their patients' genetic makeups. It's one of the most tantalizing promises of the genomic era: quick and easy tests that tell you which drugs to take or what dose is right for you.

AMPLICHIP CYP450
Roche Diagnostics

A few tests have been developed for specific diseases, such as cancer—most notably a genetic test that predicts which lung cancer patients will respond to some medications. But a new product, marketed by the Swiss pharmaceutical giant Roche and approved by the U.S. Food and Drug Administration in January 2005, now has the potential to begin making pharmacogenomics broadly accessible. Called the AmpliChip CYP450 assay, it uses genetic analyses to ascertain how quickly people metabolize certain drugs, thus predicting who is most likely to experience unpleasant or even toxic side effects.

When two people take the same dose of a drug, their bodies may metabolize it so differently that the amount of it that can act on its target varies tremendously. Some people may have an especially efficient form of an enzyme that breaks down a drug; others may have a less functional version. The AmpliChip test works by detecting specific variations in genes that code for two important drug-metabolizing enzymes, CYP2D6 and CYP2C19. These enzymes help break down 25 percent of all drugs, including the most commonly prescribed drugs in the United States, such as antidepressants, blood pressure medicines, cough medicines, and painkillers.

People with genetic variations that give them less efficient versions of the enzymes, known as poor metabolizers, could have high levels of a drug in their body for a longer period, increasing the potential for side effects. People with functioning copies of the genes are called extensive metabolizers, while people with extra copies of the functioning CYP2D6 gene are labeled ultrarapid metabolizers. "This kind of information is something every doctor seeing patients should know about," says Julio Licinio, a psychiatrist at the University of Miami's Miller School of Medicine and the editor of *The Pharmacogenomics Journal*.

CYP2D6 variations occur relatively frequently in the gene pool, though the incidence differs by population group. About 5 to 10 percent of Caucasians have a genetic profile that makes them poor metabolizers of drugs broken down by CYP2D6, whereas among Asians, the proportion is more like 15 to 20 percent. And almost 30 percent of people from North Africa and the Middle East are ultrarapid metabolizers, meaning they may need higher than standard doses of various drugs.

In addition to helping people avoid side effects, the AmpliChip might save lives. Some older antidepressants, for example, can cause cardiovascular problems if ingested in high enough doses. And while most drugs are administered in their therapeutically active form, some drugs, such as the breast cancer drug tamoxifen, must be metabolized to be effective, so they may fail to work in poor metabolizers.

"Adverse [drug] events cost the public-health system one to two billion dollars per year," says Lawrence Lesko, director of the Office of Clinical Pharmacology at the FDA. "One of the [results] is going to be prospective use of devices like AmpliChip." He adds that in the future, doctors or pharmaceutical companies could be held liable if a patient is not given a genetic test and experiences serious side effects. "I think we're going to see a huge consumer interest in pharmacogenomics," says Lesko. "And I think we're going to see more tests."

Comical Confusion

Maybe. But it's clear that the consumer boom has not yet begun. For routine blood tests such as those for high cholesterol or anemia, you stroll to a lab down the hall from the doctor's office, surrender some blood, and get a call with the results a few days later. But as I quickly learned, the sheer novelty of the AmpliChip test makes matters far more difficult. For one thing, the test is enormously expensive—I paid $1,360, though prices vary depending on the lab—and is not covered by most insurance companies. And many doctors are unfamiliar with the test and may be reluctant to order it. When I asked my doctor to have me tested, he quickly dismissed the idea. He had never heard of the test; besides, he told me,

DARRIN KLIMEK/DIGITAL VISION/GETTY IMAGES

he could figure out my optimal dose of various drugs the old-fashioned way, by trial and error.

When I finally got the opportunity to take the test (thanks to a new doctor and a subsidy from *Technology Review*), I encountered an almost comical level of confusion. Though my new, younger physician was more open to the idea, I was the first of her patients to ask about the AmpliChip, and she had no idea how to order it. I found prescribing directions on the Roche website, and a list of the few labs in the country that actually offer the test. When I called the closest one of them, a 20-minute drive from Boston, the person on the other end of the phone said she didn't know what I was talking about and hung up.

Calls to both Roche and the lab's headquarters resolved the confusion, and a few days later I arrived at a medical strip mall with a prescription from my doctor and specific instructions for the phlebotomist—"Tell her to draw seven milliliters of blood into a lavender-top tube and store it at room temperature"—lest the confusion persist. When I asked the phlebotomist how long I would have to wait in order to get the results, she replied that she had no idea. I was her first patient to get the test.

A week later, I drove to my doctor's office. She showed me a single-page document with a chart listing some of the drugs metabolized by the relevant enzymes, as well as definitions of poor and ultrarapid metabolizers. Near the top of the page was a small box containing the sum total of my results: "CYP2D6, extensive metabolizer, CYP2C19, extensive metabolizer." Much to my surprise, I am totally normal. My DNA sequences encoding both enzymes contain none of the known variants that would render them less effective in metabolizing drugs like codeine and the ingredients in NyQuil.

Did this mean I had imagined the side effects of various drugs? Were the nausea and headaches really a kind of negative placebo effect? After consulting with several experts, I still don't know the answer. Walter Koch, head of research at Roche Molecular Diagnostics, explains that a complex network of factors can influence an individual's response to drugs, including "age, gender, diet, hormone levels, concurrent medications, and inherited variations [in genes other than those tested for by the AmpliChip]."

It's also possible that I possess a rare mutation in CYP2D6 or CYP2C19, one the AmpliChip test doesn't look for. Although the AmpliChip detects the majority of known clinically relevant mutations in these genes, new variants of the genes are still being discovered, according to Miami's Licinio. Ultimately, my conundrum points out a limitation of diagnostic testing. "These tests are just one of the pieces of information that should be part of a patient's history, along with your age, your parents' medical history, and other factors," says Lesko.

Who Pays?

But at more than a thousand dollars a test, the AmpliChip is not just another easily gained piece of information. For most patients, genetic testing remains expensive and exotic, both economically and logistically inaccessible. So what will it take for pharmacogenomics information to become a standard part of our medical charts? Experts say educating physicians is one of the biggest obstacles. "When most doctors were in medical school, pharmacogenomics was not part of their training," says Licinio.

Already, though, more and more physicians do want to use these tests. David Mrazek, chair of the psychiatry and psychology department at the Mayo Clinic in Rochester, MN, uses them routinely in clinical practice. He says the benefit of pharmacogenomics in psychiatry is clear: people vary enormously in their response to antidepressants and antipsychotics, both of which can cause troublesome side effects. Some patients spend weeks or months or even years trying different doses of various drugs to find the one that brings the most relief with the fewest problems. By testing for genetic variants in drug-metabolizing enzymes, Mrazek is able to save his patients much of that trial and error. "If a patient is a poor metabolizer of Prozac, I'll start them on a different drug," he says.

The real hurdle, then, will be financial. Insurance companies still consider the AmpliChip experimental and are unlikely to cover it until large clinical trials prove that it can both help patients and cut costs. Such studies, which are already under way for psychiatric disorders, will also help determine how best to use the test.

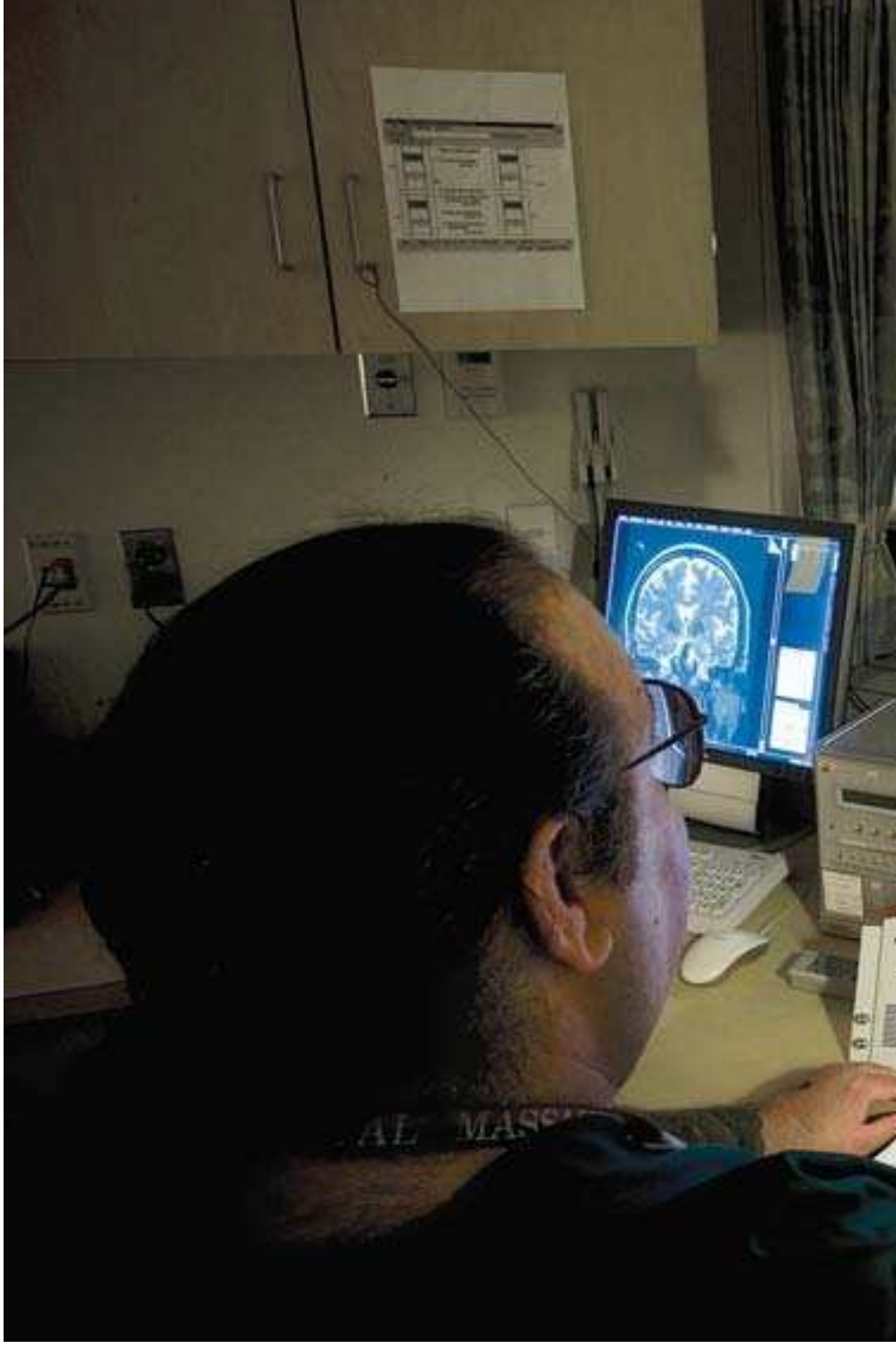
Whatever the economic and insurance considerations, however, the advent of genetic tests like AmpliChip seems all but inevitable. And for patients, that is a good thing. TR

Emily Singer is the biotechnology and life sciences editor of Technology Review.

Finding Hidden Tumors

Doctors at Massachusetts General Hospital are using whole-body MRI to illuminate a tricky disease.

By Katherine Bourzac



A green, red, black, and white 3-D image of a patient's entire body rotates on a computer screen before Gordon Harris and Wenli Cai. Harris points out a number of tumors, hallmarks of a genetic disease called neurofibromatosis (NF). Harris's research group at Massachusetts General Hospital, where he is director of 3-D-imaging services, is preparing a clinical trial to test a technique for monitoring patients, like this one, affected by NF. The technique combines PET imaging and a relatively new imaging technology called whole-body MRI. [Disclaimer: Jason Pontin, the editor in chief and publisher of *Technology Review*, serves on the board of directors of the Children's Tumor Foundation, which awarded a grant to Harris for the research described here.]

Most people have never heard of neurofibromatosis, though its three forms affect over 100,000 Americans—more than suffer from cystic fibrosis, Huntington's disease, and Tay-Sachs disease combined. About one in 3,500 babies worldwide is born with the most common form, NF1. NF1 patients may have noncancerous tumors growing along the nerves and on the skin of any part of the body. These tumors can cause pain and disfigurement; more rarely, they turn cancerous.

Much is unknown about neurofibromatosis. There are genetic tests for two of its forms, but the causes of the third, which was characterized only recently, have yet to be determined. About 10 percent of people with NF1 will develop cancerous tumors. But doctors are unable to accurately predict which patients will have a mild form of the disease, which will develop severe complications, and which will get cancer. Detecting tumors early can be difficult. "Unless you can see a tumor pressing out, or it causes a symptom like shortness of breath, we don't know it's there," says Scott Plotkin, a doctor specializing in cancers of the nervous system at Mass. General, where he collaborates with Harris. Currently, a doctor who suspects an internal tumor characteristic of NF will order a traditional MRI scan, which images only one part of the patient's body—such as the brain, right arm, or left leg—and takes about 45 minutes. In contrast, whole-body MRI can scan the entire body in 45 minutes and should find all detectable tumors at once. Plotkin and Harris's study, which starts early next year, will enroll about 250 patients and last four

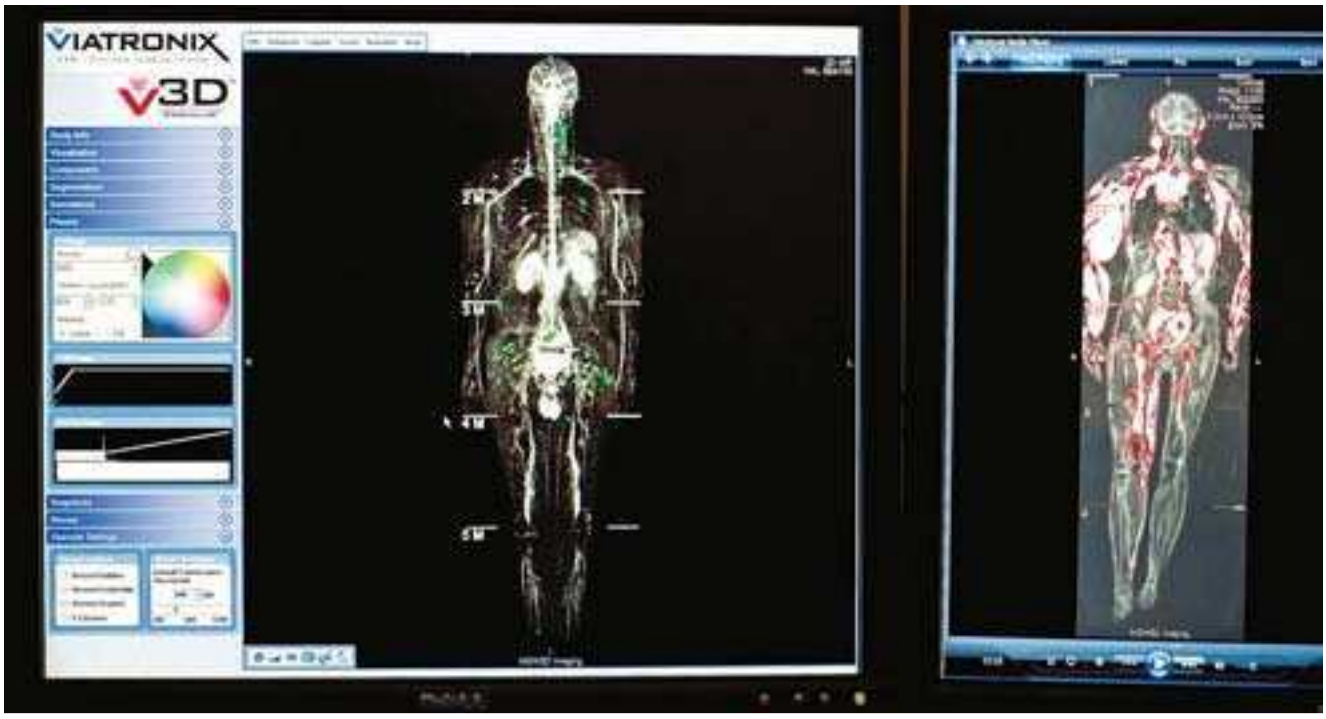
PHOTOGRAPHS BY PORTER GIFFORD

years. It will test whether whole-body MRI is able to image neurofibromatosis tumors as effectively as traditional MRI, and it will look at the effectiveness of combining whole-body MRI with PET images.

MRI provides detailed anatomical images that crisply map out the location and size of each tumor, but it doesn't reveal anything about the activity of tumors and other tissue. PET scans show how quickly tissue burns through glucose, which gives physicians a measure of how metabolically active it is. Cancerous tumors have very high metabolic rates and, says Harris, are usually "hot" on PET scans. Benign tumors have low metabolic rates, consuming glucose much more slowly.

If an NF patient's tumor becomes cancerous, Plotkin and Harris will look back at previous images to see if there were any warning signs—a metabolic reading slightly hotter than nor-

Next year, Scott Plotkin and Gordon Harris (left and right above) will begin a clinical study of a relatively new imaging technology called whole-body MRI. Using a special MRI scanner, technicians like the one at left can image a patient's entire body in about 45 minutes. Plotkin and Harris will test the technique's effectiveness in monitoring tumors associated with a genetic disease called neurofibromatosis. A whole-body MRI of a neurofibromatosis patient (top) shows extensive tumors in green.



Harris and Wenli Cai (left) designed an online database for sharing 3-D (top left, tumors colored green) and 2-D (top right, tumors outlined in red) MRI images, and PET images, from the trial. Cai is currently working to improve the 3-D-imaging software to better take into account the features of neurofibromatosis tumors.

mal. The normal range of metabolic activity for NF-related tumors is simply not known, so it can be difficult to distinguish between a tumor with a high but normal metabolic rate and one that is likely to turn malignant. Plotkin says the hindsight offered by the Mass. General trial will provide clearer guidelines for physicians about which tumors may be precancerous and should be biopsied.

Whole-body MRI is less than a decade old, and the technology is currently not part of routine patient care in the United States. But Ara Kassarjian, a Mass. General radiologist working on the NF trial, says the major manufacturers of the strongest MRI scanners used in hospitals (including Siemens, General Electric, and Philips) are now making the machines with whole-body imaging capability. The primary technological advances over traditional MRI are a table that moves a patient through the machine smoothly enough not to blur the image and software that can seamlessly weave together five or six sets of images. Researchers are testing the technique in a variety of diseases besides NF. For example, physicians hope clinical trials in progress will show whether whole-body MRI can detect the spread of cancer.

The Mass. General researchers' trial will be run in full collaboration with a hospital in Hamburg, Germany, that also treats a large number of neurofibromatosis patients and performs whole-body MRI scans. To facilitate this long-distance collaboration, Harris has built a password-protected online database where all MRI and PET images from patients at each hospital will be stored. Rather than seeing only a radiologist's report on images from the other hospital, the American and German researchers will be able to see original imaging scans from all patients. This will allow for more consistent analysis of both sets of images.

Plotkin hopes their study will take some of the guesswork out of diagnosing and managing neurofibromatosis. And in the future, he hopes to correlate the images with genetic tests, so he can better determine how gene abnormality affects the number and size of tumors in NF patients. "The ultimate goal is to understand why some patients are severely affected and others are not," he says. "This is the first step on that path." TR

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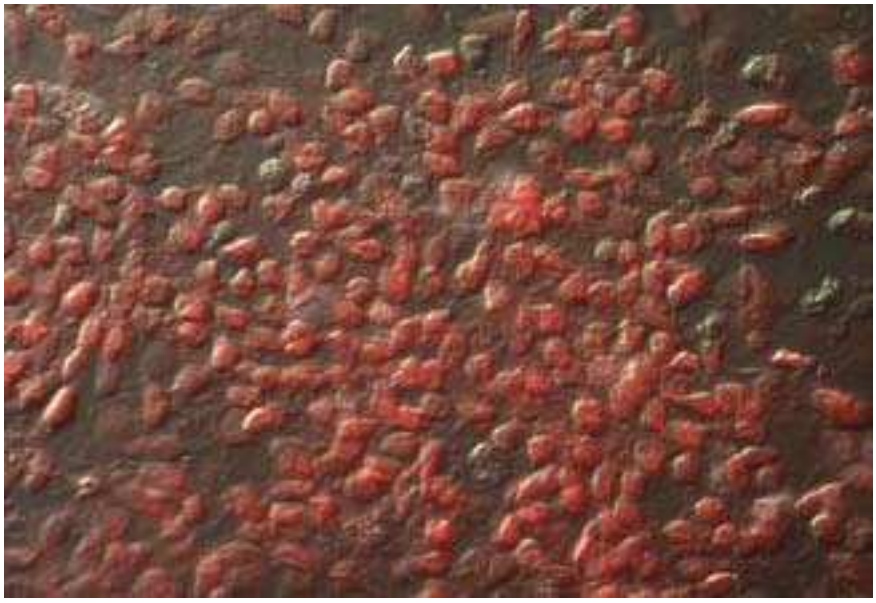

Retinal progenitor cells (pictured above) can be efficiently generated from human embryonic stem cells, providing a potential source of eye cells for transplant.

BIOTECHNOLOGY

Treating Vision Loss with Stem Cells

An efficient new method of growing retinal cells from embryonic stem cells shows promise in treating degenerative eye diseases

SOURCE: "Efficient Generation of Retinal Progenitor Cells from Human Embryonic Stem Cells"
Deepak Lamba et al.
Proceedings of the National Academy of Sciences 103(34): 12769–12774

RESULTS: Thomas Reh, at the University of Washington in Seattle, and his team have developed a reliable way to generate cells known as retinal progenitors, which have the ability to turn into any of the cell types found in the retina, such as photoreceptors or retinal ganglion cells. Preliminary results show that when the cells are transplanted into retinas either in a dish or in live lab animals, the cells migrate to different layers of the retina and begin to express proteins characteristic of the neighboring cells—including photoreceptors, which convert light into electrical signals.

WHY IT MATTERS: In retinitis pigmentosa and age-related macular degeneration, photoreceptors degenerate over time, leading to loss of vision. Previous research showed that these diseases can be treated by replacing lost cells, but there was no reliable source of replacements.

METHODS: Researchers exposed human embryonic stem cells to a mix of three proteins, called growth factors, that are involved in the development of head and eye tissue. The treated stem cells developed into retinal progenitors.

NEXT STEPS: The researchers will examine whether the cells actually restore vision when transplanted into the eye.

The Gene That Makes Us Human

A rapidly evolved piece of DNA that's unique to humans could be the key to the human brain

SOURCE: "An RNA Gene Expressed during Cortical Development Evolved Rapidly in Humans"
Katherine Pollard et al.
Nature 443(7108): 167–172

RESULTS: Researchers identified a small piece of DNA that has undergone rapid evolution in humans but not in other species, such as chickens and chimpanzees. The DNA sequence is part of a gene that codes for RNA rather than for a protein; the gene is expressed during development of the cerebral cortex.

WHY IT MATTERS: The human brain is three times the size of a chimp's—largely because of a bigger cerebral cortex, the outer layer of the brain that is responsible for reasoning and other types of complex thought. Because the newly identified variation is unique to humans, and the gene it is part of is active during cortical development, the finding might help explain how the human brain evolved.

METHODS: Researchers compared the human genome with the genomes of chimps, dogs, rats, mice, and chickens to find genetic sequences that changed little between species, suggesting that they were functionally important. Within those shared regions, the

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researchers looked for sequences that had changed significantly between chimpanzees and humans, indicating that those changes played a crucial role in human evolution.

NEXT STEPS: Researchers will try to better understand the RNA gene's role in brain development and cognition by creating a mouse that expresses the human form of the gene.

INFORMATION TECHNOLOGY

Gadgets That Know Your Next Move

Researchers have developed a model that predicts people's daily activities

SOURCE: "Eigenbehaviors: Identifying Structure in Routine"
Nathan Eagle et al.
MIT Media Lab Vision and Modeling Technical Report 601

RESULTS: Using location data, call logs, and other information collected from mobile phones, Nathan Eagle and Sandy Pentland of MIT's Media Laboratory have developed a new data-analysis technique that, with only limited initial information, can predict the daily behavior and determine the social allegiances of study participants. By looking at a few early-morning activities and locations, the researchers can forecast a person's remaining daily activities, associations, and locations with 79 percent accuracy. They can also identify group affiliations with 96 percent accuracy.

WHY IT MATTERS: As mobile devices generate increasingly immense amounts of behavioral data—about whom we call, where we go, and who is around us—they could learn to schedule meetings or recommend activities. But that will require new techniques to make sense of the data. Current computer models that predict behavior are complex and sometimes miss patterns that are simple for humans to see. The researchers' approach can characterize and predict behavior more easily.

METHODS: During the 2004–2005 school year, the researchers logged more than 350,000 hours of behavioral data collected from the mobile phones of 100 students and faculty members at MIT. The data included information on where participants were, whom they talked to on the phone, and which other participants were nearby. From this information, Eagle and Pentland extracted fundamental patterns—dubbed eigenbehaviors—that succinctly describe a person's or a group's daily activities. For example, sleeping late in the morning is part of the same eigenbehavior as going out that evening. Although the connection between these two behaviors may seem obvious to a person, it is difficult for a computer to spot using traditional behavior-prediction models.

NEXT STEPS: The researchers are looking beyond individual behaviors and group affiliations to explore people's influences on one another. They will test how well they can determine the satisfaction of people working on projects in groups, with an eye toward predicting which groups will be more efficient.

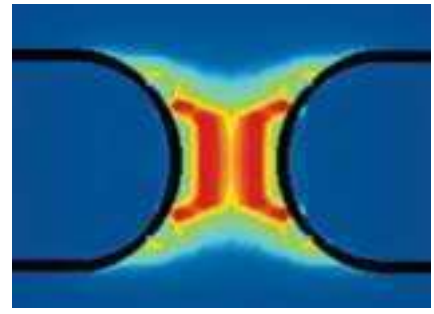
Burning Terabyte CDs

A new device that tightly focuses laser light could increase the density of optical data storage

SOURCE: "Plasmonic Laser Antenna"
Ertugrul Cubukcu et al.
Applied Physics Letters 89: 093120

RESULTS: By building a nano antenna directly onto a commercial semiconductor laser, Ken Crozier and Federico Capasso of Harvard University were able to focus light with a wavelength of 830 nanometers to a spot 40 nanometers wide. The experimental work was done by graduate students Ertugrul Cubukcu and Eric Kort.

WHY IT MATTERS: Optical discs such as CDs and DVDs are written and read using laser light. A smaller wavelength produces a smaller spot size, which allows more data to be crammed onto a disc. For instance, CDs are written and read using light with a wavelength of 780 nanometers; for DVDs, the wavelength is 650 nanometers, and for Blu-ray discs, it's 405 nanometers. That's why Blu-ray discs store so much data—up to 50 gigabytes for dual-layer discs. Traditional optical techniques use mirrors and lenses to further shrink the spot, but at best they can shrink it to half the light's wavelength. The researchers' antenna sidesteps the limits of traditional optics to produce ultrasmall spots of light that could increase storage density to about three terabytes (3,000 gigabytes) on a disc



A computer simulation of the optical nano antenna that Harvard researchers have fabricated shows two gold-coated nano rods separated by a 30-nanometer gap.

ERTUGRUL CUBUKCU

the size of a CD. Moreover, the fabrication process they developed makes it easy and inexpensive to integrate the antenna into a commercial laser.

METHODS: The antenna is made of two gold-coated nanosize rods separated by a 30-nanometer-wide gap. When light from the laser hits the nano rods, it applies a force to the electrons in the gold, nudging them out of place. The electrons oscillate back and forth, causing electrical charges to build up on both sides of the gap—positive charges on one side and negative charges on the other. The rods and the gap act as a tiny capacitor, which effectively concentrates the energy from the laser light into a spot about the size of the gap.

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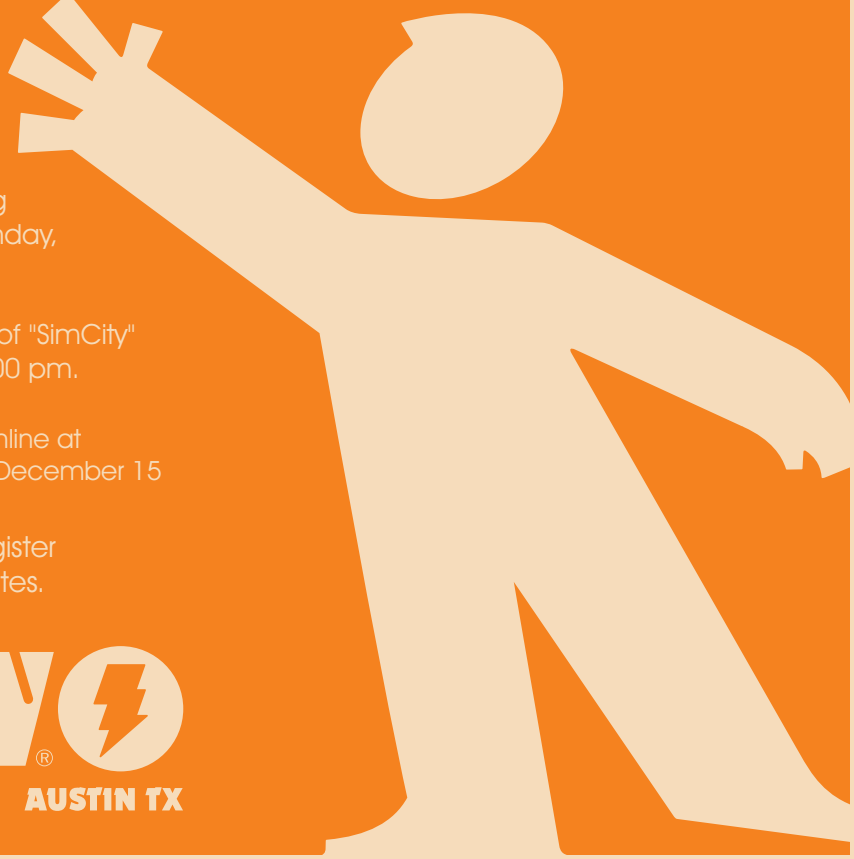

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NEXT STEPS: The researchers are exploring fabrication techniques that can decrease the gap between the rods—and the spot size—to 20 nanometers. They are also exploring alternatives to the gold that coats the rods; silver, say, could focus light more efficiently than gold at the wavelengths used in the consumer electronics industry.

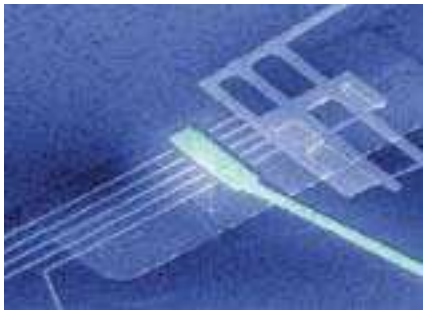
NANOTECHNOLOGY

Nanowire Computing

A practical method for nanowire-based CMOS circuits

SOURCE: "Complementary Symmetry Silicon Nanowire Logic: Power-Efficient Inverters with Gain"
Dunwei Wang et al.
Small 2(10): 1153–1158

RESULTS: Caltech researchers have made silicon-nanowire-based logic circuits similar to the complementary metal-oxide semiconductor circuits used in computer chips. Such circuits combine two kinds of transistors that respond in opposite ways to electronic signals—a useful arrangement for energy-efficient chips. Because the new method can produce both types of transistors on a single surface, it could be suitable for mass production.



This nanowire-based CMOS circuit (the nanowires are too small to see) could lead to smaller, more powerful computers.

WHY IT MATTERS: Because of their small size and excellent electronic properties, silicon nanowires could enable ultrasensitive handheld sensors for detecting cancer or identifying biological hazards. What's more, the nanowires could lead to more powerful, energy-efficient computer chips. But previous prototypes of nanowire-based circuits were made using techniques that don't lend themselves to batch processing. The new methods could make nanowire circuits practical to manufacture.

METHODS: To make p- and n-type transistors, the two types needed in CMOS circuits, researchers first created a checkerboard pattern of the p- and n-type silicon: they doped adjacent squares with different dopants, using photolithography-produced masks. Then, using a method they'd previously developed, the researchers selectively etched away silicon to form orderly arrays of nanowires. Finally, they connected these nanowires using e-beam lithography to form transistors and a fundamental type of logic circuit called an inverter.

NEXT STEPS: For mass production, the researchers will replace the e-beam lithography with the faster method of photolithography. They also need to demonstrate that an experimental process for making batches of nanowire arrays, called nano imprinting, will work in large-scale manufacturing.

Smart Nanosize Containers

Nanoparticles could signal when they are inside specific types of cells, leading to new diagnostic and treatment methods

SOURCE: "Toward Intelligent Nanosize Bioreactors: A pH-Switchable, Channel-Equipped, Functional Polymer Nanocontainer"
Pavel Broz et al.
Nano Letters 6(10): 2349–2353

RESULTS: Researchers in Switzerland have made 200-nanometer-wide containers dotted with pores whose walls are made of bacterial proteins. They demonstrated that these nano containers can control the location and duration of a fluorescent signal—lighting up only when the acidity of their environment matches that inside cell structures called lysosomes, which digest foreign materials that enter a cell.

WHY IT MATTERS: The work shows that nanoparticles using active pores can respond to environmental cues, such as acidity, to perform useful functions. In one application, pH-sensitive nano carriers would light up only once they encountered lysosomes, ensuring that they'd reached the inside of cells. The researchers earlier showed that the carriers can latch onto particular types of cells, such as macrophages, suggesting that such a system could be used to identify specific cells in a lab sample. With some modifications, it could also be used to release a drug only inside targeted cells, making drug treatment more effective and reducing side effects by protecting nearby tissue.

METHODS: Specially designed polymers combined with bacterial proteins self-assemble to form the containers, while added enzymes that break down certain compounds, causing them to fluoresce, are trapped inside. The pores' size prevents the enzymes from escaping but lets compounds gradually enter the container to be broken down, creating a long-lasting signal that is confined to the containers. The pH sensitivity is a result of two factors: the enzymes work best at lysosomal acidities, and the pores, which are open in most conditions, close at acid concentrations that are too high.

NEXT STEPS: The research requires further tests to confirm that the nanoparticles work in living subjects. For potential drug-delivery applications, the researchers will pair drugs with specific cellular targets and develop a release mechanism; it could be based on synthetic pores that stay closed in neutral and alkaline environments as well as highly acidic ones, opening only in the particular pH range of the inside of a lysosome. TR

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Gene Therapy: Proceed with Caution

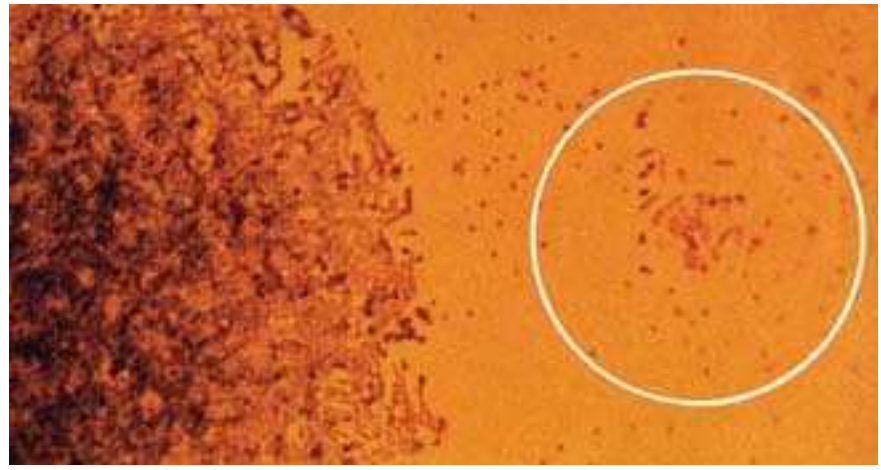
By Katherine Bourzac

In 1983, when only three genetic diseases could be detected effectively by screening tests and scientists knew very little about how genes were controlled, *Technology Review* argued that anticipated clinical trials of gene therapy would need to follow stringent guidelines, given the technology's previous failures. As Horace Freeland Judson explains in this issue *(see "The Glimmering Promise of Gene Therapy," p. 40)*, not much has changed. Caught up in the promise of curing debilitating, life-shortening diseases by giving patients good copies of defective genes—and, it seems, eager for the glory of being the first to make gene therapy work in humans—some gene-therapy researchers have conducted sloppy, and even fatal, human trials in the intervening two decades.

Judson suggests that moving gene therapy forward will require well-regulated scientific "drudgery." In April 1983, Tabitha M. Powledge suggested a similar route in her article "Gene Therapy: Will It Work?" Though she wrote two years before it was possible to mass-produce genes through the process called polymerase chain reaction (PCR) and seven years before the Human Genome Project had officially begun, the challenges she laid out sound familiar—as does the promise of gene therapy.

First, as Bob Williamson of St. Mary's Hospital Medical School at the University of London has pointed out, there are more than 2,000 single-gene disorders, and they are so diverse that most will require unique and idiosyncratic therapies. Furthermore, many are so rare that the benefits of gene therapy, if it can be achieved, may not warrant the expense, Williamson says.

Moreover, gene therapy is possible only for diseases for which the defective gene and its normal counterpart have been identified. Ways must still be found to copy normal genes in the laboratory so there will be enough to genetically manipulate and administer.



In this image from the 1983 story, thriving hamster cells at left received a healthy gene to counteract a neurological disorder, while the circled, untreated cells are dying.

In addition, the inserted gene must function properly once inside the cell and direct the production of its normal product in amounts sufficient to cure the disease without harming the patient. This final step requires detailed knowledge of how genes manufacture proteins and what turns them on and off—knowledge that is likely to be some time in coming.

Even when researchers have developed a therapy for a particular disease, clinical trials in humans can begin only after extensive trials in animals. All these criteria are likely to be observed stringently, particularly because previous attempts at gene therapy have been unsuccessful and highly controversial.

Finally, gene therapy may turn out to be applicable only to genetic disorders caused by a single defective gene, and only to some of those, Williamson points out. The technique offers no way of dealing with abnormalities of entire chromosomes, nor is it likely to be useful for the most important group of diseases—such as diabetes, heart and circulatory diseases, and many mental disorders—in which both genes and environment play a role.

In short, while the first successful gene therapy will probably burst upon the medical world before long, many scientists are pessimistic. "The correction of a disease by gene therapy will be worthwhile only if there is no other simpler and more effective technique available," Williamson says.

Baylor [College of Medicine]'s Thomas Caskey agrees that the uses of gene therapy will be limited. But he points out that many of the current treatments are unsatisfactory and do little more than ease the symptoms of disease. TR

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